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VOLUME 245 DECEMBER 13, 1951 NUMBER 24

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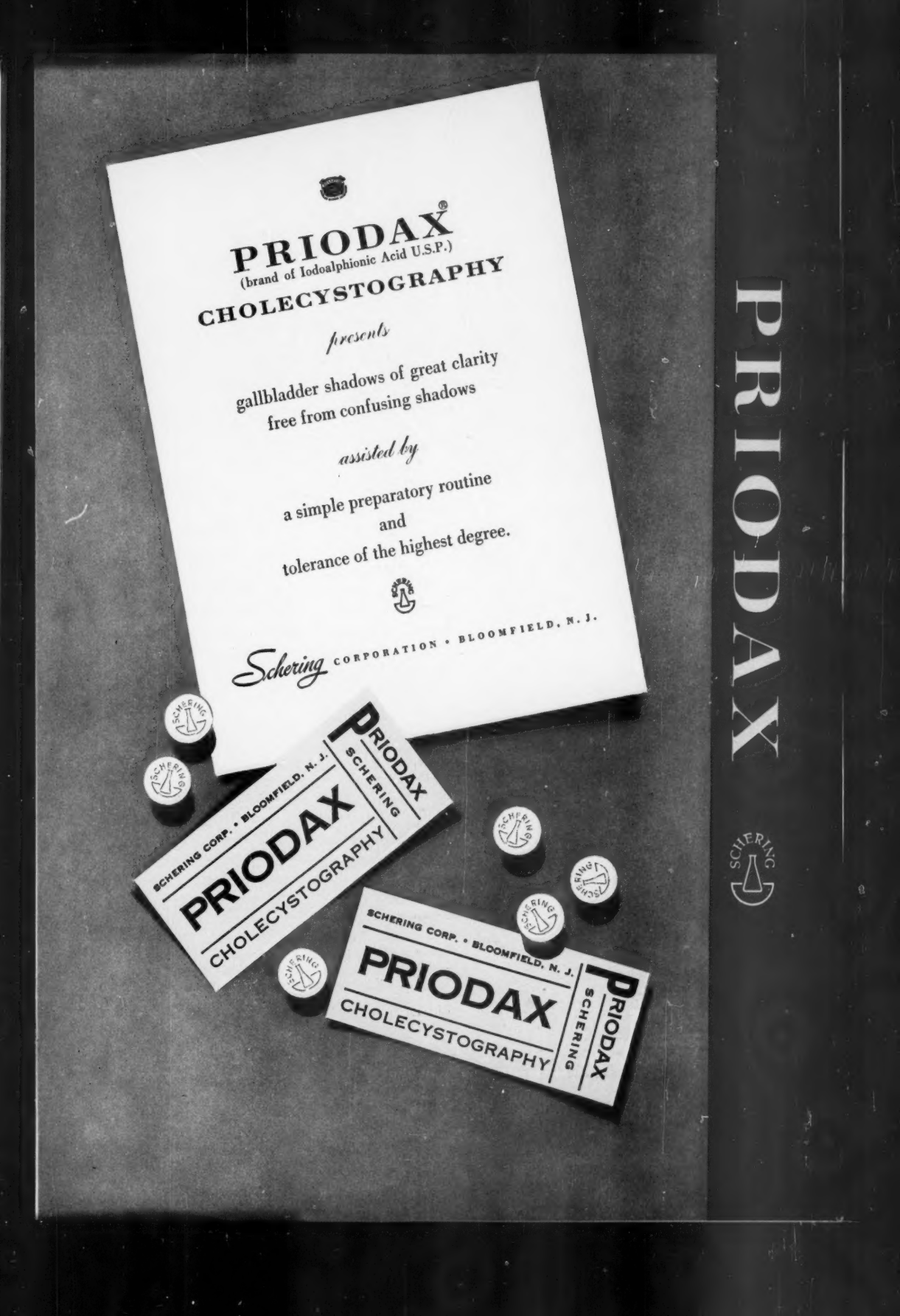
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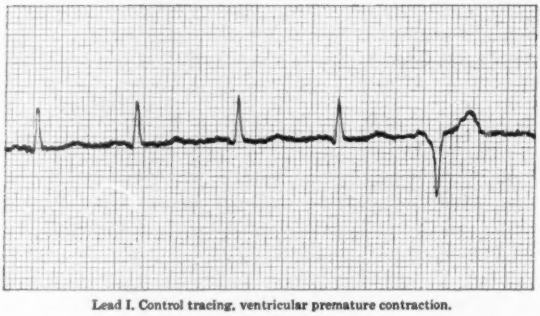

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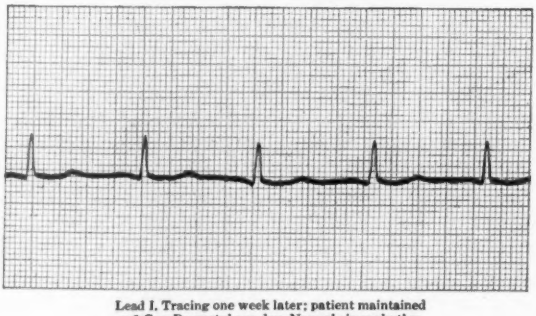

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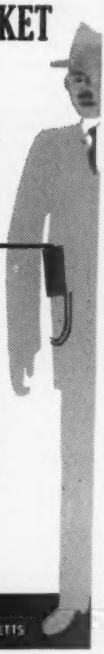

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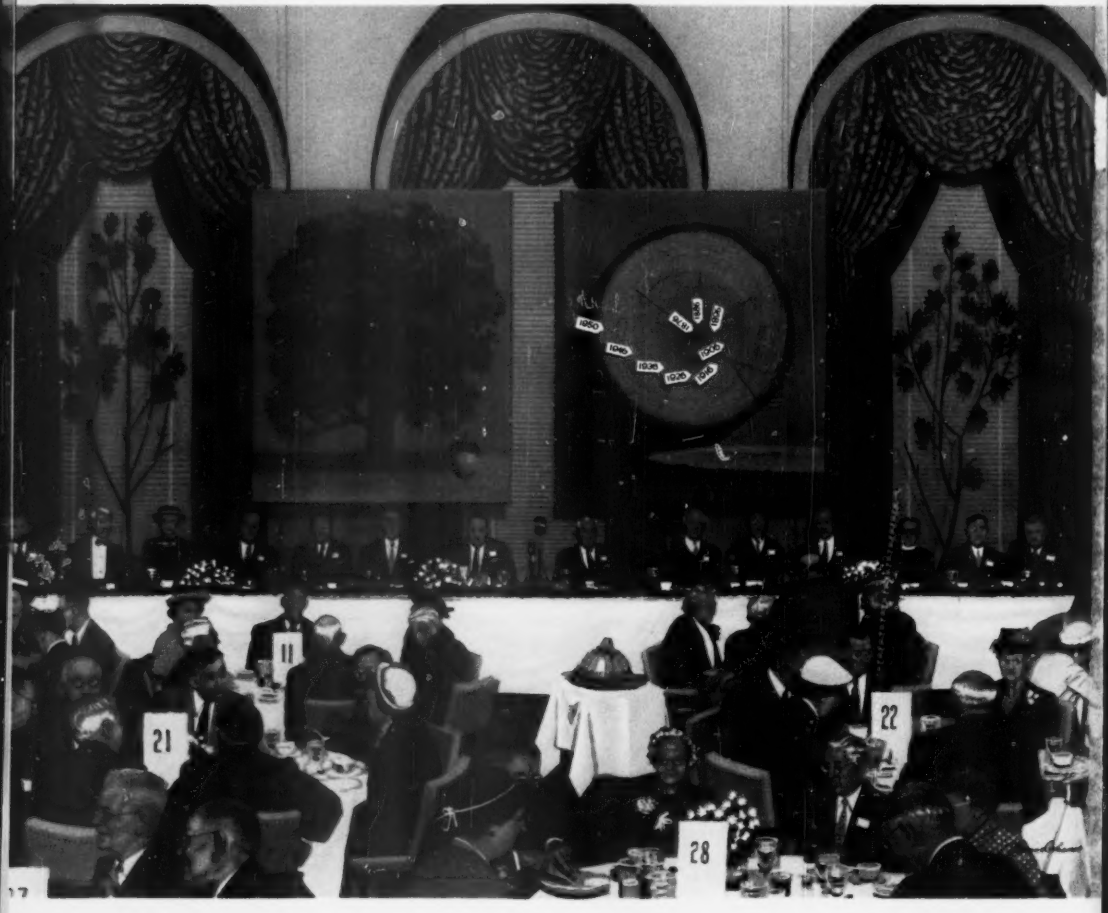

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Volume 245 DECEMBER 13, 1951 Number 24

THE EFFECT OF BAL (2,3-DIMERCAPTOPROPANOL) ON HEPATOLENTICULAR DEGENERATION (WILSON'S DISEASE)*

D. Denny-Brown, M.D.,† and Huntington Porter, M.D.‡

BOSTON

HEPATOLENTICULAR degeneration is an uncommon but not rare disease that is generally regarded as incurable. In our experience one or two cases may be found in the outpatient department of any large general hospital, often mistakenly labeled as multiple sclerosis or Parkinsonism. The more chronic type of the disease, earlier known as "pseudosclerosis" because of the prominence of an intention tremor as a symptom, is grouped with the "progressive lenticular degeneration" of Wilson, under the general heading of "hepatolenticular degeneration."[1, 2] This disease is of considerable interest, for it is one of the few chronic degenerative diseases of the nervous system in which an associated visceral disorder offers possible clues to the nature of the pathologic process. The invariable hepatic cirrhosis is of coarsely nodular type, and there is sometimes evidence of recurrent mild hepatitis. A persistent aminoaciduria is associated with the disease.[3-5]

An increased copper and silver content in the liver and kidneys in cases of the pseudosclerotic type of the disease was found in 1913 by Rumpel,[6] who first suggested that some form of "autointoxication" might underlie the disease. In 1922 Siemerling and Oloff[7] described a case of pseudosclerosis with bilateral Kayser–Fleischer rings in addition to bilateral "sunflower" cataracts, of the type seen when a foreign body containing copper lodges in the eye. Such a cataract is the condition called "chalcosis," and has been shown to be due to deposits of copper pigment on the surface of the lens.[8, 9] It is of special interest that chalcosis can be also accompanied by a green ring of copper pigment under Descemet's membrane, in the position occupied by the Kayser–Fleischer ring.[10] Siemerling and Oloff[7] suggested that the disease could be due to accumulation of copper salts in the viscera, eye and nervous system. Studies of the metallic content of those tissues were at first inconclusive. Vogt[11] and others strongly advocated the theory of silver intoxication, but it now appears likely that abnormal findings in relation to this metal were due to the prevalent use of silver salvarsan in treatment of nervous diseases in that period.[12] Gerlach and Rohrschneider[13] in 1923 failed to find silver in the eye by spectroscopic tests but found traces of copper in the cornea. A marked increase in copper content of both brain and liver was shown by Haurowitz[14] and by Glazebrook.[15] Cumings,[16] in the first controlled study, has compared these tissues with those in other types of hepatic disorder; he found quantities of copper varying from 39.4 to 156.5 mg. per 100 gm. of dry tissue in the liver in Wilson's disease, compared with a normal range of 3.7 to 17.2 mg. In the basal ganglia the values in Wilson's disease were 69.5 to 71.6 mg., compared with normal values of 6.1 to 12.0 mg. per 100 gm. Iron was not increased beyond the normal range. In a case of multilobular cirrhosis the copper content was not increased in liver and brain. A chance observation of Mandelbrote and his associates,[17] in the course of an investigation of the mobilization of copper by BAL in multiple sclerosis, that one of their controls, who had Wilson's disease, showed a high urinary output of copper in a single determination, greatly increased by BAL, suggested to us that any such mobilization of the excess of body copper in this disease would be of interest. Cautious exposure of two patients with hepatolenticular degeneration to injections of BAL, with coincident estimation of urinary copper and alpha-aminoacid nitrogen showed that despite a sevenfold increase of urinary copper induced by BAL the aminoaciduria was not changed.[5] This suggested that the abnormal copper metabolism is either secondary to the aminoaciduria or independent of it. Both patients had been severely incapacitated by their neurologic symptoms. It was noted that one patient was less tremulous in the second week following the exposure to BAL, but the change was not greater

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than those occurring as natural variations of symptomatology of the disease. In the following five months, however, it became clear that this change for the better was maintained. This finding was mentioned in a preliminary report on the chemical aspects of this study in 1949.[5] With an improved method a high resting urinary output of copper was a consistent finding in four cases compared with adequate controls.[18]

Treatment by dietetic regulation having previously been attempted without effect and no other method of influencing the course of the disease being available, we were encouraged to repeat the use of BAL in these patients, with resulting further improvement. In view of the pharmacologic finding that toxic effects of large dosage of BAL in the normal organism[19] included hepatic damage, a close watch for further impairment of hepatic function was maintained. Toxic effects of repeated increase in copper excretion and of depletion of other metals were possibilities. These fears proved to be groundless. Five patients have now been treated with BAL for long periods, with most striking results. A demonstration of 3 of these patients at the annual meeting of the American College of Physicians in April, 1950, has stimulated others to use this method of treatment in various centers, and reports of clinical improvement have reached us. We now report a survey of prolonged treatment of our own 5 cases after sufficient exposure to BAL and chemical studies to provide a firm basis for estimation of the rationale and objective of treatment of the disease by this means.

Method

The estimations of urinary copper were made by a modification of the method of Eden and Green.[18] The avoidance of metallic contamination of the specimen is of paramount importance; we are greatly indebted to the many house officers and residents of the Neurological Service of Boston City Hospital who have undertaken the difficult task of collecting uncontaminated urine in violently tremulous patients. The estimations of serum iron were kindly arranged for us by Dr. W. B. Castle, those of alpha-amino nitrogen by Dr. C. S. Davidson, of the Thorndike Memorial Laboratory.

Case Reports

Case 1. M. G., a 21-year-old married woman, was first seen in June, 1949, suffering from tremors of the limbs of 2 years' duration. There had been no previous illness of note and no pregnancies. The patient was an only child, and there was no history of neurologic or hepatic disease in the family. In November, 1946, there had occurred a transient episode of shaking of the left hand, which reappeared in April, 1947, after which the entire left arm began to shake on any purposeful movement. By August, 1948, writing had become impossible. At this time the presence of the brownish-golden ring of pigmentation of the cornea was recognized, and a high-carbohydrate, low-fat, low-protein diet was instituted. The tremors worsened, and stiffness appeared in the lower limbs in the following months. By June, 1949, the patient had commenced to have difficulty in rising from a chair, as well as diffuse rigidity and slurred speech. She was unable to hold a drinking vessel without spilling the contents and unable to get food to her mouth with a fork, because of the tremor. At rest the limbs were held stiffly, without tremor. With the limbs outstretched a regular tremor at the rate of approximately 3 per second commenced at both wrists. The left hand was held in an athetoid posture. There was titubation of the head when unsupported and a mild rigidity of plastic type in both lower limbs but no tremor. No clinical evidence of disordered hepatic function was found.

The patient was given stramonium and later tolserol and continued a less strenuous high-carbohydrate diet, but her movements continued to become slower. By October, 1949, her head nodded violently, even when resting against a pillow, and the rigidity of the limbs, particularly on the left, had become so intense that she could not get out of bed or turn over in bed without assistance. She could stand or take a few steps only with considerable assistance; she now had to be fed. Her speech was difficult to comprehend. Her facial expression was fixed; movement of the eyes, lips and tongue was slow. The mouth was held partly open, and swallowing of saliva was impaired. The left hand was held in a fixed athetoid posture, with continual flexion-extension tremor at the wrist and interphalangeal joints. The right arm was less rigid and showed less tremor at rest but became violently tremulous on movement at the wrist and shoulder. A rhythmic tremor at the left ankle was present during attempted movement and at times at rest. There was no loss of power to resist passive movement, but all active movement was slow and difficult. The tendon reflexes were difficult to elicit because of rigidity; the abdominal reflexes were present, the right plantar response flexor and the left equivocal. A broad, opaque, dark-brown Kayser–Fleischer ring of pigmentation of the cornea was obvious in both eyes without special illumination. No other pigmentation was found. The liver margin was barely palpable on deep inspiration. There was no jaundice and no evidence of ascites or of vascular spiders.

Laboratory tests revealed a hemoglobin of 14.5 gm., 4,350,000 red cells and 10,250 white cells. The urine showed no trace of sugar or albumin; urinary alpha-amino nitrogen by the ninhydrin method was 133–146 mg. in 24 hours. This is within the normal range (100-200 mg. daily). The cephalin-flocculation test was + (Hanger's method, normal + to + +), the thymol turbidity was 5.9 units (normal, 0-5), the zinc turbidity 3.9 cc. (normal, below 2.4 cc.), the formol-gel test was 0 and the bilirubin 0.15 in 1 minute, total 0.57 (normal, below 1.0 mg. per 100 ml.). In view of these insignificant abnormalities, it was surprising that a liver biopsy showed part of a grossly degenerate lobule, separated by a fibrous septum from an actively regenerating lobule.

The patient was given three courses of BAL intramuscularly in October, 1949, each in the form of doses every 4 hours of 1.6 cc. (2.5 mg. per kilo of body weight, of a 10 per cent solution in peanut oil) each for 24 hours, at intervals of 5 days between courses. The only immediate effect was a brief frontal headache at the end of the first course. The collection of urine was difficult because of the patient's tremor and restlessness, but the results of copper estimations on the few complete 24-hour specimens collected by catheter in glass receptacles showed that the resting output of copper was increased (310 microgm. per 24 hours) and further raised more than sevenfold in the first 24 hours of dosage of BAL (2665 microgm. per 24 hours), falling rapidly to twofold in the next 24 hours. A total of 8 mg. was excreted on the 3 days BAL was given.*

The patient was discharged on October 28, with no apparent change in her clinical condition. Two weeks later a remarkable improvement began, with a general lessening of rigidity and tremor. By December 6, when she was next seen, the patient was able to get up from a straight chair unaided, could sometimes place a particle of food in her mouth with her right hand and could walk a few steps unaided. She was able to turn over in bed. By January 19 she was able to bend over and pick up an object from the floor and could eat slices of orange unaided but still could not hold a cup or glass without spilling. She could not undress herself or put on stockings. Her appetite was good, and she had had no gastrointestinal symptoms at any time. Some frequency of micturition had been the only visceral symptom. The left hand was no longer athetoid, but some persistent

*With the improved method of estimation used since February, 1950, these values would be slightly less.

rigidity still slowed alternating movements. Violent tremor of the limbs occurred only when the patient was excited or nervous. Speech was less explosive but still slurred.

In mid-February, 1950, there had been little change since mid-January, and the patient was readmitted to the hospital for further review and liver-function tests. A blood count and standard urine tests revealed no abnormality. The urinary amino nitrogen was 295, 264 and 420 mg. in 24 hours on three different occasions. The prothrombin time was 17.4 seconds (73 per cent), the bromsulfalein retention 0 in 45 minutes (normal 0 to 4 per cent) and the thymol flocculation negative (normal 0 to +). The cephalin flocculation, zinc flocculation and the formol-gel test were negative; the total serum protein was 6.8 and the albumin-globulin ratio 3.9/2.9. The resting urinary copper output in 24 hours was 251 microgm. A further course of BAL, in three 24-hour periods separated by intervals of 5 days, was given in February, 1950. The only reaction was subjective and in the nature of nausea and a generalized itchiness of the skin during the second course. The estimations of urinary copper at this time are shown in Table 1 and in graphic form in Figure 1. By March 9 the patient found that she could raise her arms and put her hands behind her head. The tremor of the hands continued, but she could at times hold out the left hand for a brief interval without tremor. On March 3 the urinary alpha-amino nitrogen was 264 mg. in 24 hours.

In the following weeks the patient found that she could sit for progressively longer periods without tremor of the head and could walk longer distances without fatigue. By May 9 she could brush her teeth, dress herself and fasten large buttons and could, when alone and unexcited, drink from a glass. She was still unable to hold a cup without spilling, could not write and could not eat with a fork without hurting herself. The tremor of the hands was obvious only on special testing and when the patient was under stress. The plantar responses were both flexor. The Kayser–Fleischer rings were now less opaque but occupied about the same width of the uppermost part of the cornea, being more faint at the lateral and inner margins.

By June 29, 1950, the tremor had worsened a little in the preceding three weeks; titubation was present at times when she was sitting, and some dysarthria had returned. There was no evidence of anemia or of hepatic insufficiency. A further course of BAL in three 24-hour exposures was given. Nausea and dizziness were prominent. In the next month there was again improvement to the previous level, with additional freedom of movement; she could now take long walks alone and help with housework. The dysarthria had almost disappeared. In September, 1950, the improvement had been maintained except that some difficulty in fastening buttons had again returned. There was no tremor at rest. Tremor of the right hand and some titubation of the head occurred in walking, and the left hand was held stiffly. Liver-function tests gave values approximating those previously obtained. A further course of BAL was given, again with resultant nausea and dizziness. In the following months gains were slight but continuous until December, when a fall resulted in a worsening of tremor, even at rest, for one week, followed by recovery to her previous status. There was now only occasional tremor of the outstretched right arm and none of the left. Speech was distinct. Walking was free and natural, but with occasional dystonic stiffening of the right leg. The patient could drink from a glass of water, spilling only a few drops, and could brush her hair. In Janu-

TABLE 1. *Urinary Copper Content in Patients with Wilson's Disease.*

M. G. (CASE 1)			J. G. (CASE 2)			A. G. (CASE 3)			E. R. (CASE 4)			R. F. (CASE 5)		
DATE	COPPER CONTENT		DATE	COPPER CONTENT		DATE	COPPER CONTENT		DATE	COPPER CONTENT		DATE	COPPER CONTENT	
	microgm./100 cc.	*microgm./24 hr.*		*microgm./100 cc.*	*microgm./24 hr.*		*microgm./100 cc.*	*microgm./24 hr.*		*microgm./100 cc.*	*microgm./24 hr.*		*microgm./100 cc.*	*microgm./24 hr.*
1950			1950			1950			1951			1950		
2/7	20.4	251	2/10	28.6	582	2/6	54.0	713	5/8†	53.9	831	10/3*	86.8	1040
												1951		
2/11	20.0	207	2/11	27.0	448	2/9	51.7	674	5/26	18.0	422	1/4	35.6	565
2/22*	73.8	1460	2/22*	56.3	1971	2/22*	152.4	1679				5/14	19.6	256
2/24	16.1	224	2/23	20.2	573	2/23	72.8	812				5/23†	41.2	929
2/26	17.8	216	2/24	18.1	534	2/24	49.3	715				7/10	27.5	318
2/27*	121.0	1453	2/26	19.6	560	2/26	40.4	481						
3/1	16.2	272	2/27*	85.3	1535	2/27*	95.8	1446						
3/3	15.3	167	3/1	24.9	667	3/1	40.1	538						
1951														
1/25	21.5	187	3/3	18.4	465	3/3	30.1	476						
2/1*	38.2	1058	3/4*	85.6	2282	3/4*	127.7	1970						
5/4	11.7	215	3/5	46.5	948	3/5	60.6	785						
5/15†	28.2	650	3/6	25.0	566	3/7	45.4	656						
			3/8	20.6	475	3/8	37.5	682						
			1951			1951								
			4/21*	73.1	1581	5/26	38.1	711						
			5/4	33.8	494									

*Exposure to 4-hourly injections of BAL during the period of collection.
†Two injections of BAL in the 24-hour period.

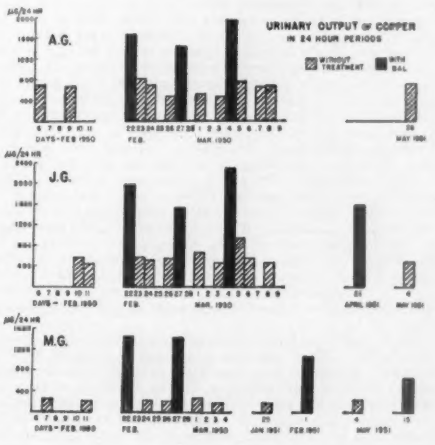


FIGURE 1.

ary, 1951, the tremors again increased, with resulting greater difficulty in feeding herself, renewed tremor at rest and occasional coarse tremors in the left shoulder and in both hands when outstretched. At times there was also tremor in the head, trunk and thigh muscles. There was no change in laboratory data, except that the urinary alpha-amino nitrogen had returned to a low value (114.6 mg. per 24 hours). A further identical course of BAL was then given, with no reaction other than nausea on one occasion. In the following months improvement again occurred, and by May, 1951, she could peel an orange, wash dishes and walk long distances again. The resting urinary copper excretion continued unaltered (M. G., Fig. 1). She could feed herself with a spoon, turn the pages of a book and occasionally drink from a glass of water, although she preferred to use a straw for drinking. There was occasional tremor of the hands at rest, and on finger-nose test the tremor of the left hand tended to become violent on repetition. The patient walked a little stiffly, with slight tremor of the left hand and occasional locking of the left knee. The plantar responses remained flexor. Slight rigidity could be felt in the right lower limb on manipulation. Mental ability remained unimpaired, and no sensory disorder had appeared. The Kayser–Fleischer rings were still obvious, about 1 mm. in width in their uppermost part and deep brown in color, but thin and transparent elsewhere; the iris could be seen clearly through them. General medical examination revealed no abnormality, except that the liver border was palpable one fingerbreadth below the costal margin. An estimation of serum iron was reported to be 60 microgm. per 100 cc. (normal 50-180 microgm.). The patient was given 1.7 cc. of BAL twice daily for 10 days. She has maintained her status without further objective change since that time, except that the tremor is now seldom violent, with a further 10-day course of BAL in July, 1951.

CASE 2. J. G., a 37-year-old Italian-born former truck driver, had been under the observation of the Neurological Unit since 1947. His case was reported at length by Uzman and Denny-Brown[3] in 1948. One brother (Case 3) is similarly affected. Two sisters are unaffected. In 1943, at the age of 30, he had noticed some tremor of the left hand when he raised the hand to his lips. A few months later the right hand showed the same tremor on movement. In the next 2 years the tremors of the hands gradually became worse, and in 1945 an occasional side-to-side tremor of the head was noticed when he was under any stress. In that year he had to give up his occupation of driving a truck because of the tremor. In the following year his speech became noticeably slurred, and the tremor manifested itself on any movement of the upper limbs. The patient was then unable to write or to shave or feed himself. In 1947 he presented a gross tremor of the extended hands, including elements of flapping flexion-extension at the wrist and also at the shoulders. Moderate titubation of the upper trunk and head was evident when he stood unsupported, and his gait was slightly reeling in character, with severe titubation. A broad smoky-brown Kayser–Fleischer ring (about 3 mm.) was present in each cornea, and a dense brownish-gray sunflower cataract had been present in the left eye as long as he could remember. A liver biopsy showed mild regenerative activity without fibrosis. A battery of liver-function tests gave negative results, except for a +++ response in the zinc-flocculation test. A marked aminoaciduria was present. The patient was discharged on a low-fat, high-protein, high-carbohydrate diet.

In the following 3 years the condition of the patient slowly deteriorated. There was still no clinical evidence of hepatic disorder. When he was completely relaxed with the limbs supported there was no tremor, but by 1950 any attempt to use the hands or raise the head resulted in violent tremor. The lower limbs were still unaffected, and except for slight ataxia and the continued tremor of the upper part of the body the gait was unaffected. On examination the patient exhibited a mild euphoria. Speech was slow and scanned and was difficult to understand. The head was inclined continually to the left. The liver and spleen were not palpable. The output of alpha-amino nitrogen in the urine was 405 to 533 mg. in 24 hours. The cephalin flocculation was now +++, as was the zinc flocculation. The prothrombin time was 80 per cent. The total serum protein was 5.7. The bromsulfalein retention was 12 per cent in 45 minutes. The spinal fluid showed no cells, but the Pandy test was +, the total protein 54 mg. per 100 cc. and the colloidal gold 3333221000. There was mild renal glycosuria, which, together with aminoaciduria, was studied by Cooper and others.[4] In February, 1950, the urinary alpha-amino nitrogen was reported to be 450 mg. and 533 mg. per 24 hours on two occasions. An electroencephalogram showed normal rhythm.

The patient was given BAL, 2 cc. every 4 hours for six doses on February 23, 1950. This was repeated three times, at intervals of 4 days and 5 days, without reaction. The urinary copper output before BAL and in response to BAL is shown in Table 1 and Figure 1 (J. G.) By March 9 the patient expressed considerable subjective improvement. He stated that he felt more relaxed, his speech was easier and there was less tremor of the head; he walked more steadily and could use a urinal without spilling the contents. When he was seen again in the first week of April, his speech was only slightly scanned and he could sit erect without tremor of the head. Tremor was still marked in the finger-nose test but was greatly improved. He was still unable to feed himself but could write shakily and shave. Later the same month the tremor again increased in intensity, after some emotional stress, and continued so until July, 1950, when he was readmitted to the hospital. On this occasion a + albuminuria with granular casts was found. The cephalin and zinc flocculation tests gave the same response as before. The prothrombin time was 64 per cent and the bilirubin .02/.35. The bromsulfalein test showed 50 per cent concentration in 2 hours. Urine urobilinogen was positive (1:4). A second course of BAL was given, 2 cc. 4-hourly for 24 hours, twice repeated at intervals of 2 days. In the following month the patient again became able to feed himself and his speech was clearer, but he could not shave or write. After 2 months his speech again became less clear, and by October, 1950, his tremor again prevented his feeding himself. His serum iron content at this time was 135 microgm. per 100 cc. He was given a further identical course of BAL in November, 1950, but after this he noticed only slight improvement. He became extremely depressed and anxious, and to the observer his tremor remained at the same intensity, although both tremor and speech were better than a year previously. It was difficult for him to perform a finger-nose test without violently striking his face. With simple reassurance and some planning of his home activity he improved to his status of November. About February, 1951, he again developed a gradual worsening of his tremor; in the following two months he became unable to brush his teeth or comb his hair, and by April he had great difficulty in dressing himself and his dysarthria again made his speech difficult to understand. He remained cooperative and intelligent but exceedingly tense and anxious. The Kayser–Fleischer rings had assumed a distinctly gray appearance, but their width was not altered. He could lie relaxed without tremor, but when holding a posture a gross irregular tremor of the upper limbs and gross titubation appeared. He could still walk and run but awkardly and with gross deviations. He could drink from a straw and could eat a piece of fruit but could not feed himself from a plate. He could not write. There were still no altered reflexes. There was now no glycosuria. A battery of liver-function tests showed no essential change since his earlier reports.

He was given 4 further 24-hour series of injections of BAL in April, without reaction. In May the tremors were again less violent and he returned to the status of July, 1950.

CASE 3. A. G., a 42-year-old man, the elder brother of J. G. (Case 2), had been employed as a cloth cutter until the onset of a tremor of both hands at the age of 29 years. Within a few months of the onset of tremor his head was observed to shake from side to side. The tremor had gradually worsened. In 1947 the patient had suffered a mild head injury in an automobile accident, after which he had noticed stiffness of his legs, with awkward gait and many falls. In the following 3 years he had suffered from occasional attacks of loss of consciousness lasting about 10 minutes, at frequent intervals. His memory had become grossly defective, and his prevailing mood was euphoric. When first examined by us in January, 1948, he showed a fixed facial expression, with periodic severe tremor of the upper limbs and head at rest that was greatly aggravated by movement. Speech was slurred and difficult to understand. There was plastic rigidity

of all the limbs; the tendon reflexes were all brisk, with ankle clonus and bilateral extensor-plantar responses. The gait was grossly ataxic on a wide base, with a tendency to fall backwards. The skin showed bronze pigmentation. A very broad, deep smoky-brown Kayser–Fleicher ring was present in both corneas (shown in a photograph in the report of Uzman and Denny-Brown[2]). The liver was not palpable and there was no clinical evidence of cirrhosis. The spinal fluid showed no cells; the total protein was 90 mg. per 100 cc., the Pandy test + and the gold sol low midzone. There was a +++ albuminuria and + renal glycosuria. The total urinary alpha-amino nitrogen was 404 and 430 mg. per 24 hours on two occasions. The aminoaciduria of this patient was further investigated by Cooper and others (1950). He was readmitted to the Neurological Service in March, 1949. His movements had become slow and stiff, and he had to be assisted to rise from bed and to walk. He was otherwise likely to fall backwards. Severe tremor still occurred on movement. Liver-function tests revealed no defect. In particular the cephalin-flocculation test was 0, the prothrombin time 100 per cent and the icteric index 10. The glycosuria persisted, with ++ albuminuria. The resting urinary output of copper was 23 microgm. per hour. The patient was given 2.2 cc. of BAL intramuscularly every 4 hours for 6 doses and an additional single injection of 3.6 cc. (7 mg. per kg. of body weight) was repeated twice at intervals of 5 days. The resulting eightfold increase in copper has previously been reported.[b] The patient reacted to the smaller injections with nausea and vomiting, which also occurred with the larger dose. A mild hematemesis after the larger dosage caused the treatment to be stopped at this point. The patient also complained of some haziness of vision at this time. These symptoms subsided within a few hours, and after a week he felt subjectively much improved and could rise from bed and walk unassisted.

In the following months the tremor gradually lessened and disappeared. No further fainting spells occurred. The gait remained ataxic and slow. By the end of 1949 the tremor returned when the arms were used, and in February, 1950, it was decided to attempt a further exposure to BAL. There was a divergent strabismus. Speech was still slurred. Memory was poor and initiative was impaired. There was no tremor on sitting, with the limbs supported, and only mild titubation on standing. The finger-nose test showed severe incoordination and striking of the face. Muscular strength was unimpaired, but a moderate Parkinsonian rigidity was present in both upper and lower limbs. The patient walked with legs wide apart and without associated movements. The plantar responses remained extensor. An electroencephalogram was normal. The blood count revealed no significant abnormality. A + albuminuria was present, with a trace of sugar. The fasting blood sugar was 117 mg. per 100 cc., and a glucose-tolerance test showed a high curve of diabetic type. The prothrombin time was 100 per cent, and a series of liver-function tests gave negative results. The bromsulfalein-retention test showed a faint trace after 45 minutes. The serum protein was 8.4 mg. The urinary alpha-amino nitrogen varied from 404 to 430 mg. in 24 hours.

On February 22, 1950, BAL (1.8 cc., 4-hourly, for six doses) was given intramuscularly; this was repeated on February 27 and March 4. The urinary output of copper is shown in Table 1 and Figure 1. Nausea, vomiting and malaise occurred on each occasion but were not severe. A marked improvement was already manifest by March 9; the patient could shave himself for the first time in 10 years and could drink a glass of water without spilling a drop. By the beginning of April he showed only a slight terminal tremor in the finger-nose test with either hand. His speech was slurred but could easily be understood. His intellectual function had not improved. The rigidity in the limbs appeared unchanged and his gait was still grossly ataxic, but he was less prone to lose his balance. The reflexes were unaltered. This improvement was maintained until June, 1950, when he again became slower in movement and liable to falls. Occasional incontinence of urine occurred, and the patient was at times confused. In July, 1950, a battery of liver tests still showed no abnormality. The liver edge was palpable 2 cm. below the costal margin. A glucose-tolerance test showed 127 mg. per 100 cc. fasting, rising to 155 in ½ hour, 318 mg. in 1 hour, 228 mg. in 2 hours and 139 mg. in 3 hours. There was variable (negative to ++) glycosuria, no acetone and no albuminuria. The urobilinogen was negative. No esophageal varices could be demonstrated at barium swallow. There was no anemia. The patient was unable to tolerate the full dosage of BAL but was given 26.1 cc. in 6-hourly 1.4-cc. doses over a period of 5 days, followed by 9.1 cc. in a period of 3 days in the following week in June, 1950. Two weeks later he already could walk more steadily and his tremor again became less, being only provoked by the finger-nose test or prolonged standing. He was no longer incontinent, and his speech, though slow, was more intelligible. His mental powers remained greatly impaired.

In October, 1950, he began again to fall and to show occasional urinary incontinence. He was given a third course of BAL at reduced dosage (three 24-hour exposures, each 6 injections of 1.0 cc., without reaction). In the following months he regained ability to dress himself, shave, attend to his toilet, tie shoestrings and walk without support. His walking again lapsed during March, 1951. In April, 1951, BAL was given twice daily for 12 days; this was repeated for a further 10-day period in June. This has also produced improvement, but the mental impairment persists. His memory is very poor. Both plantar responses remain extensor, although pseudobulbar manifestations have not appeared. His writing is barely legible. He can feed and dress himself but is careless and is still occasionally incontinent. These changes are of the type related to mental apathy. Slight tremor is occasionally present. The Kayser–Fleischer rings are more gray than formerly but not otherwise changed. The liver is smaller, but hepatic tests show no change. In spite of the bronze pigmentation of the skin and the glycosuria, the serum iron was found to be 120 microgm. per 100 cc. in December, 1950, but a raised level (183 microgm.) was found for the first time in May, 1951.

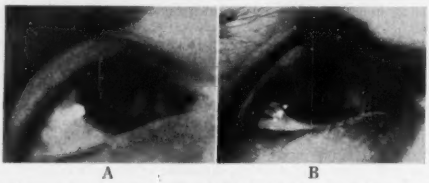
Case 4. E. R., a 26-year-old mechanic of Italian descent, was first admitted to the Neurological Service of Boston City Hospital in September, 1945, complaining of difficulty in speech and swallowing and of tremor in the right arm and leg. The only previous illnesses had been a convulsion at the age of 2 years and rheumatic fever at the age of 15. A sister has suffered from convulsions since childhood. The patient showed no residual cardiac disability. In September, 1944, at the age of 20, he had first noticed increasing difficulty in enunciating words clearly and difficulty in disposing of excess saliva. In the following months he began to have difficulty in fine movements and in writing with his right hand. In July, 1945, after an emotional upset, he noticed a rhythmic tremor of the right leg and arm at rest. On examination at that time he was irritable, with expressionless facies, except for a facile and prolonged smile, and a slight drooping of the left corner of the mouth. His speech was slurred and nasal. There was no tremor of the arms at rest, but all movements of the right hand were poorly co-ordinated, and a coarse intention tremor was present in this limb. The left foot showed some dystonic spasm in plantar flexion in walking. A definite brownish Kayser–Fleischer ring of pigmentation in the outer margin of each cornea was confirmed by slit-lamp examination. Liver-function tests at that time revealed a prothrombin time of 82 per cent and a ++++ cephalin-flocculation test but no other abnormality. The patient was emotionally unstable and left the hospital against advice. He attended other hospitals from time to time, but his symptoms continued to worsen. In 1946 tremor appeared in both upper limbs in all attitudes except complete relaxation, and his speech became so dysarthric as to be unintelligible. In 1947 the right hand began to maintain a constant clenching, and he was unable to relax the fist except by a series of flinging movements with this limb. Rigidity of the right limbs and trunk gradually became more manifest, and by May, 1949, when he was next admitted to Boston City Hospital, he had great difficulty in changing position or in walking. He sat or stood with his body and neck forward, his mouth open, drooling saliva. The upper limbs were held stiffly flexed against the body, the right hand clenched and the wrist flexed. A slow undulating tremor of both upper limbs and usually of the lips was present at rest. He was able to make jerky movements with the left upper limb and with the proximal joints in the right upper limb. It was evident that a strong grasp reflex was present in both hands. There was no loss of power of resisting passive movement in any part, but all movements were greatly impeded by strong rigidity of Parkinsonian type. The tendon reflexes were all present and active, and there was bilat-

eral ankle clonus. The abdominal reflexes were present. The plantar responses were equivocal. The liver dullness appeared to be diminished. There was no jaundice or other evidence of liver disease. The blood count was normal. The urine showed ++++ albumin and a minimal trace of sugar. The resting urinary output of copper was 11 microgm. per hour; this increased to 101 microgm. per hour in the first hour after a single dose of BAL, 4 mg. per kg. of body weight (2.56 cc.), given intramuscularly. This single injection did not disturb the patient, and no change in his neurologic condition was noted. A few days later, after a dental extraction, the patient suffered prolonged discomfort from a dental abscess. When this had been treated he was discharged for convalescence.

In the following months the patient gradually became more rigid; by April, 1950, he was unable to rise from a chair and unable to walk or to feed himself. On readmission to the Neurological Service he now lay on one or the other side or could be sat in a chair, with flexion of all limbs and chin sunk on his chest. The mouth gaped open, drooling saliva. He was able to communicate only by indicating letters on an alphabet held near his left hand. The right hand was held either open or tightly shut, the left hand usually clutching the bedclothes. With any attempted movement a rhythmic tremor of the shoulders actuated both upper limbs. When the patient was irritated or impatient a violent tremor of the right arm would appear, the limb beating against the body, with titubation of the head. Rigidity was usually intense in all the limbs, being more marked in the flexors than in the extensors. Power of resistance to passive movement was present in all the limbs, and there was no contracture. The tendon reflexes were present and active, the abdominal reflexes absent and the plantar responses both extensor. There was no disorder of sensation. Dark-brown Kayser-Fleischer rings were well marked. At this time the patient developed cystitis, and further treatment with BAL was deferred.

By June 3, 1950, the patient had recovered from the cystitis but was now extremely drowsy and was completely unable to swallow. The liver could be percussed only over 3 fingerbreadths. Spider angioma was present over the chest. The stools were brown in color and natural in appearance. There was no bile in the urine. The cephalin-flocculation test was ++++, the total serum protein 5.3 gm. per 100 cc.; the albumin-globulin ratio was 2.5/2.8 and the prothrombin time 42 per cent. BAL, 1.7 cc. intramuscularly, was given six times in 32 hours with no reaction, and this was repeated three times at intervals of 3 days (3.06 gm. in 8 days). Four days later the patient was much less lethargic; in 3 more days he was able to swallow. By June 27 tube feeding was discontinued. He was then able to move his limbs to turn in bed, but he had great difficulty in communicating even simple needs. On June 29 and July 3 and 6, he received three further courses of BAL, each of six injections of 1.7 cc. at 4-hourly intervals, without reaction. By July 10 the patient was able to communicate rapidly by pointing out letters on an alphabet and was able to walk with support. His features were less rigid, and he was attentive to what was said to him. By July 16 he could write slowly but legibly with a pencil. By the end of August he could walk alone. He was given a further full course of BAL (three 24-hour exposures) in September, after which he continued steadily to improve; by January, 1951, he could run, walk backwards, turn and attend to all his toilet needs except combing his hair. He could then brush his teeth and feed and dress himself. Speech, in the form of slow guttural sounds, returned. His writing was now intelligible and coherent. In May, 1951, he found that his lower limbs were again stiffening and requested further treatment. The copper content of the urine at this time is shown in Table 1. He now presented some general rigidity and absence of expression except a slowly developing smile, with occasional tremor of the left angle of the mouth. There was no tremor of the outstretched arms. He spoke in a monotonous, guttural voice. He walked in slow, awkward fashion, advancing the right limbs slowly. The limbs were all slightly rigid, the right more so than the left, with very brisk reflexes, including grasp reflexes and tonic foot responses. There was great splenic enlargement, and the liver was palpable 2 fingerbreadths below the costal margin. The Kayser-Fleischer rings were possibly more translucent than previously but were otherwise unchanged. He continued to show moderate hepatic impairment. The cephalin-flocculation test was ++++, the bromsulfalein retention 24 per cent and the total serum protein 5.0 gm. per 100 cc., with an albumin-globulin ratio of 3.8/2.2. He was given a course of BAL, 2.0 cc. twice daily of a 10 per cent solution of BAL in oil for 13 days, without reaction. A month later his speech, walking and writing had increased in speed, but in July trembling of the arms became troublesome, necessitating further treatment.

CASE 5. R. F., a 47-year-old woman, had had side-to-side shaking of the head for 12 years and tremors of the hands and dysarthria for 10 years. One sister had died at 25 years of age from "acute yellow atrophy of the liver." She had had to give up teaching school 8 years earlier because of these disorders; at that time she had become unable to write or to feed herself. For 5 years she had had difficulty in maintaining her balance when walking. There had been occasional bouts of anorexia and vomiting but no jaundice. In 1944 she had had irradiation for a uterine fibroid, without complication. Speech and gait had steadily worsened in 1949 and 1950. By September, 1950, there was marked fixity of expression, an explosive cerebellar type of dysarthria that made her speech unintelligible and a marked rigidity of all limbs, with titubation of the head and trunk, that made it impossible for her to walk or to stand without assistance. The outstretched limbs developed a widely inco-ordinate tremor, and it was not possible for her to touch her finger to her nose without violent flinging movements. Tremors of the head and limbs continued at rest. The tendon reflexes were brisk and equal, the plantar responses flexor. The liver was not palpable. There were deep-brown Kayser-Fleischer rings, 2 mm. wide. Laboratory tests revealed no glycosuria or abnormality in glucose tolerance. The serum iron, inorganic phosphorus and calcium were within normal limits. The cephalin flocculation was ++, the zinc flocculation ++ and the thymol turbidity 12.02 units, indicating mild hepatic insufficiency. The urinary alpha-amino nitrogen was reported to be 134.1 mg. per 24 hours and 147.1 mg. per 24 hours on two occasions. A course of three 24-hour exposures to BAL was given in September, 1950, without reaction or immediate change. A steady improvement began late in October with a lessening of tremor and improvement in speech. By December, 1950, she could dress herself and walk alone but still could not feed herself. There was now no tremor if the head and limbs were supported. Her writing was still illegible. Renewed liver tests showed no change. The urinary alpha-amino nitrogen was reported to be 232.8 mg. per 24 hours. In December a further full course was given (2 cc. 6-hourly for 36 hours, repeated three times at intervals of 2 days). Estimations of urinary copper content are shown in Table 1. By March, 1951, she was able to drink from a glass of water without spilling, could write (shakily) for the first time in 10 years and could go out shopping alone. A further full course of BAL was then given; this was repeated in April and May, 1951. In this period rapid improvement continued. She became able to insert a key into a lock or a coin into a slot, could do her own cooking without spilling and was able to walk as much as 5 miles. A further course of BAL, twice daily for 10 days, was given in May, 1951, and it was recommended that this be continued every second month. In July the patient signed a letter legibly, saying that improvement steadily continues and that she can now draw a glass of water from a faucet and drink it with one hand, without spilling. The Kayser-Fleischer rings became distinctly gray (Fig. 2).



A B

FIGURE 2. *Two Photographs of the Right Eye in Case 5. A = taken September 22, 1950. B = taken May 17, 1951. Photograph B slightly overemphasizes the grayness of the corneal ring as it appeared in May, compared with the more diffuse golden-brown haze seen in A.*

Discussion

The substance 2,3-dimercaptopropanol (British Anti-Lewisite, BAL) was originally introduced by Peters and his colleagues[20-22] as an antidote for the effects of arsenic gases. In a series of brilliant investigations these workers showed the effect of arsenic in combining with –SH groups in certain tissue proteins and the effect of BAL in competing with the tissues for arsenic. BAL reacts with arsenoxides to form nontoxic compounds that are rapidly excreted. BAL has since been shown to promote excretion of other metals such as mercury,[23] gold,[24, 25] silver and copper.[17, 26] There is some evidence that the excretion of any excess of copper in the system takes priority over that of other physiologically important metals such as iron or zinc.[27]

In the present investigation the effect of BAL is seen as clearly related to a mobilization of copper deposited in the tissues. An excessive resting urinary output of copper has been found in every patient suffering from hepatolenticular degeneration whom we have examined. With a refined technic the resting level, before exposure to BAL, has ranged from 207 to 713 microgm. per twenty-four hours. These values, referred to by Porter,[18] are taken from our Cases 1 to 4. Case 5 of this report showed values of 318 to 565 microgm. per twenty-four hours. With the same method and the same care to avoid contamination of the urine, the output in a series of normal controls was found by Porter[18] to be 0 to 14.7 microgm. per twenty-four hours. The effect of four-hourly injections of BAL, in a ratio of 7 mg. per kg. of body weight, has been to raise the resting urinary output from 2 to 7 times in the first twenty-four hours, with a rapid fall on the second day and a return to resting level on the third or fourth day (Fig. 1). This change had no effect on the natural fluctuation of aminoaciduria that has been always associated with the disease in our cases. No evidence of toxic reaction other than the transient nausea, dizziness and occasional vomiting and blurring of vision commonly associated with administration of BAL was encountered, in dosage up to 2.5 mg. per kg. of body weight. In Case 3, a single injection of 7.0 mg. per kg. resulted in severe vomiting, hematemesis and blurring of vision. We therefore used the smaller dosage, at times reducing it by as much as one half to avoid severe nausea. It is important to ensure that the injections are deeply intramuscular and not made near nerves, as subcutaneous injections cause painful lumps. Since May, 1951, we have changed the routine of injections to twice daily for ten or twelve days. This has been more convenient to the patients, and estimation of copper output on the tenth day (Table 1 at †) showed a continued high output.

All 5 patients presented are clearly suffering from the more chronic "pseudosclerotic" type of hepatolenticular degeneration, with a history of tremor in the upper limbs and dysarthria, progressing to titubation of the head and trunk, and dystonic rigidity. The age of onset has varied from nineteen to thirty-five years, and the illness had run a course of from four to thirteen years before causing the patients to require assistance in eating, dressing, toilet and walking. Improvement after a course of BAL usually begins fourteen days after the course and continues for the next two to three months. Two of the 5 patients had become unable to move without assistance. All are now believed to have derived maximum improvement, but they continue to require maintenance treatment. All are able to take care of themselves, with the exception of the patient described in Case 3, in whom intellectual and physical deterioration had reached a severe degree before regular exposure to BAL was instituted.

At the beginning of this investigation it was not known whether the mobilization of copper in this manner would lead to further damage to the liver, and a close watch was kept for evidence of hepatic impairment. The few signs of hepatic insufficiency already present showed no change that was considered significant after multiple exposures to BAL. As we gained confidence, the intervals between exposures to BAL were lessened. There was no evidence of a deficiency of iron or of other minerals resulting from prolonged administration. It will be apparent from the histories of the first 4 cases that the improvement resulting from exposure to BAL began to relapse in three to six months after each treatment. Tremor and dysarthria again increased, again to be lessened by further exposure to BAL. Such changes were not associated with any change in the resting urinary output of copper (Table 1), which appeared to maintain a steady individual level for each patient. It is therefore probable that each course of BAL removed some excess deposit of the metal in the tissues and that renewal of symptoms was related to renewed deposition.

The work of Haurowitz,[14] Glazebrook[15] and Cumings[16] established that the liver and brain are the site of such deposition of copper in hepatolenticular degeneration, and that of Gerlach and Rohrschneider[13] shows that the Kayser–Fleischer ring is, at least in part, visible evidence of such deposition in the cornea. The brown pigmentation of the lenticular nucleus in the brain is likely also to be due to copper. It is therefore of clinical interest that the Kayser–Fleischer rings in two of our patients have lost much of their brownish coloration, becoming more gray (Fig. 2). In the younger patients the ring has appeared to become more translucent, but this change is more difficult to establish. Newell and others[28] have shown that BAL is effective in removing intraocular copper experimentally introduced, and it appears that its effect on the Kayser–Fleischer ring, as found by us, is further evidence of the ring's cuprous nature. The sunflower cataract

in the left eye of Patient 2 is extremely dense, and no visible change has occurred in it.

We estimate that the net total copper mobilized during one three-day course of BAL was about 3 to 4 mg. This would amount to approximately half the copper content of the normal liver but is only about 5 per cent of the content of the liver in Wilson's disease. Attention should be drawn to the delay before clinical improvement occurs, which suggests that a shift in bodily distribution of the copper takes place. Mandelbrote and his associates[17] found that in normal rats prolonged exposure to BAL reduced the copper content of the liver greatly but had little effect on that of the brain. The residual amount per gm. of tissue was similar in both organs, suggesting to us that the residue was a more resistant physiologic form of copper.

Van Ravensteyn[29] has found that in the normal person the excretion of copper parallels the intake in the diet, being from 1 to 2 mg. per day. The chief route of excretion is the bile. Since the resting urinary output in hepatolenticular degeneration is greatly elevated, we immediately suspected that the cirrhotic liver was failing to excrete copper in the bile in this disease. This, however, is not the case, for specimens of bile from 3 of our patients, collected with extreme care to exclude copper contamination, proved to contain from 8.3 to 19.8 microgm. per 100 cc. of copper, within the range of normal values (5.6 to 31.0 microgm. per 100 cc. by our method). The increased urinary output must therefore reflect a disorder of absorption of copper, such that an excess of the metal is present in the serum, accumulates in the tissues and overflows a renal threshold. Glazebrook[15] found a raised serum copper content. In these respects the fundamental overabsorption of copper appears to be comparable to the overabsorption of iron now proposed as a basis for hemochromatosis.[30-32] Indeed, the coincidence of hemochromatosis and of hepatolenticular degeneration has been reported by Kuipers,[33] but this must be rare. Even in the presence of glycosuria and bodily pigmentation in Cases 2, 3 and 5 we have found no abnormality of serum iron content, except for a recent borderline value in Case 3. A skin biopsy in Case 3 was negative for hemochromatosis. The question of the importance of copper in the pathogenesis of hepatic cirrhosis (raised by Mallory[34, 35]) is reopened by the present work, although no answer can at present be given.

Aminoaciduria has been present in all our cases, and we presume that fluctuations such as that found in our Case 1 account for the isolated observation of absence of aminoaciduria in a case reported by Cumings.[36] Since the aminoaciduria is not affected by mobilization of copper, it is to be regarded as an independent reflection of the derangement of enzyme systems that must underlie the disease. Cooper and his associates[4] concluded that both the aminoaciduria and the glycosuria in our Cases 2 and 3 represented a defect in renal threshold. The original observations of Uzman and Denny-Brown[3] of slightly raised serum alpha-amino nitrogen and the subsequent development of a diabetic type of blood-sugar curve in these patients appear to us to indicate hepatic and pancreatic defects. Dr. Edward Kass of the Thorndike Memorial Laboratory has kindly estimated the glutathione concentrations on the whole, oxalated blood of our Patients 3 and 4 before and after a twelve-day course of BAL. The estimation was carried out at various oxygen tensions. No abnormality was found, indicating that the glycolytic systems within the erythrocyte were not distributed by the disease or by its treatment by BAL. There is as yet no clue to the nature of the fundamental defect.

It is particularly remarkable that long duration of symptoms does not deny reversibility of the process. Spielmeyer[37] has long since shown that pigmentation and glial proliferation are the chief pathologic alterations of the more chronic pseudosclerotic forms of the disease. Extensor plantar responses, pseudobulbar manifestations and intellectual defect document the severe cavitations that occur more frequently in the younger patients with more rapidly progressive forms of hepatolenticular degeneration. Less improvement may be expected when such lesions have occurred. Thus we may learn that for even the most chronic of "degenerative" diseases there is a reversible part that Peters[20] aptly terms the "biochemical lesion."

We have presented substantial evidence that the neurologic symptoms of hepatolenticular degeneration are related to the abnormal accumulation of copper compounds in the brain. The similarity of the resulting tremors and rigidity to those of manganese and mercury intoxication indicates a site of action common to this whole group of compounds. In hepatolenticular degeneration regularly repeated maintenance injections of BAL are necessary, as it does not appear feasible to eliminate copper from the diet. From our present data a course of twice-daily injections of 1.0 to 1.5 cc. of BAL in peanut oil for ten days every second month appears to be adequate. In the beginning such courses may be given once a month until a steady clinical status is reached. It is obvious that the earlier in the course of the disorder this can be instituted the more complete the reversal of symptoms that can be expected. This finding in a "degenerative" disorder that is commonly familial gives substance to the hypothesis that all such nervous diseases result from the cumulative effects of by-products of "inborn errors of metabolism" and offers hope for the ultimate solution of their problems.

Conclusions

A prolonged study of 5 patients suffering from hepatolenticular degeneration subjected to repeated courses of BAL has established a direct relation

between an abnormal accumulation of copper compounds in the liver and brain in this disease and the neurologic symptoms. The tremors and rigidity are reversible, sometimes to a remarkable degree, after repeated mobilization of bodily copper by this method. The use of BAL in treatment of the disease and inferences concerning its pathogenesis are discussed.

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THE USE OF HEPARIN-GELATIN-DEXTROSE IN VENOUS THROMBOSIS AND PULMONARY EMBOLISM*

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BOSTON

THE chief obstacles to the wide-scale use of heparin in the treatment of venous thromboembolic disease are two: the expense of the available commercial heparin preparations and the transiency of action of this drug however injected in the usual aqueous solutions. The short-lived action of heparin has necessitated constant venoclysis or numerous separate injections for its administration and numerous clotting-time determinations for its close regulation. The many workers in this field have appreciated that these obstacles of expense and short-lived action could be circumvented simultaneously if the effect of a single injection of heparin could be made to last over many hours.

In 1942 Loewe, Rosenblatt and Lederer[1] demonstrated in rabbits the marked prolongation of action of heparin by its incorporation in Pitkin's menstruum. Bryson and Code[2] in 1944, using heparin in beeswax, were able to maintain coagulation times in dogs in most cases at therapeutic levels for from seventeen to seventy hours. In 1945 Lange and Boyd,[3] and later Weiner and Lange,[4] showed that the addition of ephedrine and adrenalin to a heparin-gelatin-dextrose mixture definitely lowered the rate of clotting-time rise and prolonged the action of the heparin in the deposit. Series of patients suffering from thromboembolic disease were successfully treated with heparin in Pitkin's menstruum by Evans and Boller[5] and by Loewe and Hirsch.[6] After experimenting with heparin in various retarding media, Vorzimer and others[7] concluded that a cholesterol-derivative–peanut-oil–beeswax mixture was the most satisfactory.

Intramuscular injections of highly concentrated aqueous-heparin solutions (100 to 200 mg. per cc.), administered two or three times daily, were reported by Stats and Neuhof[8] to prolong the clotting time for periods of eight and twelve hours.

McCleery, Artz and Sirak[9] reported the "potentiation" of a given dose of heparin by orally administered caronamide. Caronamide, by blocking the renal excretion of heparin, increased the height of clotting-time response but did not prolong the effect.

Of these methods designed to prolong the action of heparin, known drawbacks exist in the use of certain depository media. Beeswax tends to produce sterile abscesses.[2] Peanut-oil–beeswax mixtures may cause pulmonary embolism.[10] Eucupin and chlorbutanol as anesthetic agents are often added to Pitkin's menstruum to combat the pain commonly felt after injections of this medium. Intramuscularly given concentrated sodium heparin, which eliminates the need for any medium, must be injected at least three times daily. Accordingly, it was hoped that the use of the gelatin-dextrose mixture would prove to be the most practical method of heparin administration. This would call for only one injection of the drug daily and only one or two clotting-time determinations daily and would probably require the smallest dose of heparin.

Therefore, during the twenty-month period from February, 1949, through September, 1950, 100 surgical patients with thromboembolic disease were treated with heparin-gelatin-dextrose (depo-heparin) as the sole anticoagulant agent. During this same period approximately 100 additional thromboembolic cases were treated variously with subcutaneous aqueous heparin, heparin and Dicumarol combinations or by vein division. This second group of 100 patients, miscellaneously treated, is not the concern of this report except for those cases representing failures of depo-heparin therapy who were further treated by other anticoagulants or by vein division.

MATERIAL

The ages of these patients, closely paralleling similar reported series, are listed in Table 1.

Eighty-nine of these patients were diagnosed as having deep venous thrombosis, including 20 patients with accompanying pulmonary embolism. Eleven were diagnosed as having pulmonary emboli without evident signs of venous thrombosis. This incidence of pulmonary embolism without leg signs (35 per cent of pulmonary emboli) is in close accord with the experience of others, and it should be again stressed that the lack of leg signs should not militate against the diagnosis of pulmonary embolism. It has been repeatedly shown that the great majority of such cases if untreated will demonstrate definite leg signs as time passes.

METHODS

The use of any heparin preparation has always entailed difficulties in establishing the proper daily dosage for a given patient. In 1943 de Takats[11] stressed the great individual variations in reactions to heparin and the varied reactions in the same pa-

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tient from day to day. He showed that in the immediate postoperative period most patients exhibit a greater tolerance to heparin and that patients with deep venous thrombosis will almost invariably display a marked increase of tolerance to heparin. This tolerance will diminish as the days pass or as treatment progresses. Tuft and Rosenfield[12] and Hagedorn and Barker[13] confirmed this finding of increased heparin tolerance in thromboembolic patients. Our earliest patients were treated with 400 mg. of heparin-gelatin-dextrose, 200 with and 200 without vasoconstrictors, with the idea that this would maintain them for forty-eight hours. We immediately found three difficulties with this

Table 1. *Ages of 100 Patients with Thromboembolic Disease Treated with Depo-Heparin.*

Age Group	No. of Patients
10–20	5
20–30	10
30–40	7
40–50	18
50–60	24
60–70	24
70–80	10
80–90	2
	100

dosage: The clotting times at six or eight hours were often alarmingly high, in the range of two to three hours. Bleeding was apparent in 2 such cases, and we thought that such high clotting times were undesirable. The heparin effect did not often last over thirty hours — sometimes not over twenty-four. The resultant clotting-time curves were double-humped, adding to the difficulty of regulating the patient's clotting-time level. These facts led us to discard the heparin without the vasoconstrictors as adding nothing but confusion and an increased tendency to bleed. As a result, 94 per cent of the patients reported here received only heparin-gelatin-dextrose with vasoconstrictors. All clotting times were determined by the Lee–White method, chiefly by the same two technicians.

As an aid in arriving at a suitable daily dose of heparin, the last 77 patients in this series were tested for their tolerance to heparin by a modification of the method of de Takats.[11] A base-line clotting time was obtained, after which 25 mg. of sodium heparin was given intravenously. Further clotting times were carried out twenty, forty and sixty minutes later, and the resultant clotting-time curve was utilized to determine the initial dose of heparin. If the peak of this curve fell below twenty minutes, the initial dose was usually 300 mg. If the peak of the curve fell between twenty and fifty minutes, the patient was given 200 mg. of the drug. If the peak of the curve was over fifty minutes, we used, for the most part, a 100-mg. dose. By this method, 10 patients were found to be unusually tolerant to heparin, and in practice 7 of these required larger doses than the 200-mg. "normal" to produce satisfactory clotting-time levels. Similarly, 51 patients showed average (twenty to fifty minutes) test curves. Of this group only 1 patient required more than the 200-mg. dose, and only 2 patients were found to need less. Of the 16 patients who seemed to be sensitive to heparin on testing, only 7 were truly so, in that they maintained satisfactory clotting-time responses on only 100 or 150 mg. of heparin daily. Had these 7 patients been given the usually accepted daily heparin dose, it seems reasonable to suppose that some of them would have bled. The actual heparin dosage given these patients is shown in Table 2.

Ideally, with the use of heparin the patient's clotting time should be maintained at 2 to 4 times normal. Exact attainment of this goal is impossible by any means we have at present. The work of Bauer[14] and others has shown fairly conclusively that excellent results are obtainable with heparin even though the clotting time is not constantly above normal. Utilizing twice-daily clotting times in these patients, — with which the six- or eight-hourly true clotting-time peak is often missed, — we have been content if our apparent clotting-time peaks have fallen between fifteen and forty minutes. By this standard 6 of these cases showed clotting-time peaks of over forty minutes, 80 fell between

Table 2. *Depo-Heparin Dosage in 100 Patients with Thromboembolic Disease.*

Heparin mg./day	No. of Patients
100	7
150	6
200	76
250	1
300	9
350	0
400	1
	100

fifteen and forty minutes and 12 were unsatisfactorily low, namely, under fifteen minutes. Interestingly enough, none of the unsatisfactory results were obtained in this last group. Clotting-time determinations were not made in 4 patients because of the condition of their veins. These patients were treated for an average of 7.3 days.

Complications of Therapy

Two patients complained of nausea, palpitation, numbness and tingling of the extremities, hot flashes and some blurring of vision shortly after a heparin injection. It is difficult to say whether these symptoms were due to a primary heparin effect, as described by Chernoff,[15] or to that of the vasoconstrictor substances. Two patients developed

gluteal *Staphylococcus aureus* abscesses that required incision and drainage. Pain at the injection site has not been troublesome with the use of this heparin preparation. Many of the patients questioned thought that the heparin injection was no worse than a penicillin injection. Approximately 50 per cent of the patients complained of a lingering soreness at the site of the deposit that tended to subside in twenty-four to forty-eight hours. A few patients complained rather strongly of pain after the injections, but in no case was it necessary to discontinue the treatment because of discomfort.

The search for an allegedly perfect anticoagulant, namely, one that will never cause bleeding, is almost certainly futile. Any substance that lessens the coagulability of the blood will render likely the occasional escape of such altered blood from vessels that are damaged by disease or injury — surgical or other. Heparin preparations are, of course, no exception to this, and it is remarkable how infrequently allusions are made in the literature to bleeding from heparin and how relatively rarely are such cases reported.

In this group of patients, 4 bled from the operative site alone, a fifth bled from the operative site and elsewhere and a sixth bled from the urinary tract. Two additional patients had mild epistaxes while receiving heparin, but in neither case was the anticoagulant regimen altered or stopped. Brief case histories of the first 6 patients follow:

Case Reports

Case 1. C. O. (No. 5B309), a 33-year-old woman, underwent a subtotal thyroidectomy after preparation with ACTH. The ACTH was discontinued on the third postoperative day; on the following day the patient had a sudden episode of right chest pain, with pain and tenderness in the left calf. There was a past history of thrombophlebitis of the left leg. A chest film showed a definite pulmonary infarct. A heparin-tolerance test showed a peak of 1 hour and 55 minutes, despite which she was given 200 mg. of heparin-gelatin-dextrose with vasoconstrictors and 200 mg. without them. Twenty-one hours later, at a clotting time of 2 hours, she developed a large wound hematoma. Approximately 30 cc. of bloody fluid was aspirated from the wound, and an additional 30 cc. later escaped spontaneously. She was given 25 mg. of protamine sulfate intravenously on three occasions at 6-hourly intervals, during which 8 clotting times were over 15 minutes. Dicumarol therapy was then instituted and maintained for 11 days without further difficulty.

Comment. This patient was given too much heparin and too little protamine. The bleeding in this case could have been avoided by more careful attention to heparin dosage.

Case 2. A. J. (No. 2C633), a 47-year-old woman, developed a deep venous thrombosis in the right calf on the seventh day after abdominoperineal resection of the rectum for carcinoma. No heparin-tolerance test was made. A baseline clotting time was 7 minutes. She was given 200 mg. of heparin-gelatin-dextrose with vasoconstrictors and 100 mg. without them. Ten hours later, at a clotting time of 130 minutes, the patient began to bleed from the gums, the perineal wound and the colostomy and into the subcutaneous tissues of the chest wall and back. A blood transfusion was given and oxycel packs were used to control the oozing; 12 hours later the clotting time was 10 minutes. All bleeding had ceased.

Comment. This patient received too large a heparin dose. Furthermore, the large granulating wound contraindicated the use of heparin in a deposit.

Case 3. A. K. (No. N1854), a 52-year-old woman, had a vaginal hysterectomy. Four days later the signs of deep venous thrombosis appeared in both legs. A heparin-tolerance test showed a 40-minute peak. She was given 200 mg. of heparin-gelatin-dextrose with vasoconstrictors and 100 gm. without them. Eight hours later the clotting time was 35 minutes, at which time she had a vaginal hemorrhage of approximately 200 cc. Fifty mg. of protamine sulfate was given intravenously and repeated 5 hours later. This promptly controlled the bleeding.

Comment. Even though this clotting-time level is in the therapeutic range, the heparin dosage was too large.

Case 4. H. C. (No. 45957), a 54-year-old woman, developed a deep venous thrombosis in the right leg on the seventh day after a total hysterectomy. The heparin-tolerance test showed a peak of 15 minutes. The patient was given 200 mg. of heparin-gelatin-dextrose with vasoconstrictors; 16 hours later she showed moderate vaginal bleeding. The clotting time was 13 minutes. Eight hours later the clotting time was 10 minutes, and the bleeding stopped spontaneously. Because of recurrence of signs in the leg 4 days later the patient was reheparinized for 5 additional days, receiving 200 mg. a day, with entirely satisfactory results.

Comment. The bleeding in this case was unavoidable.

Case 5. A. C. (No. 5B88), a 32-year-old woman, showed the classical signs of pulmonary embolism on the fourth day after a total hysterectomy. She was given 200 gm. of heparin-gelatin-dextrose after a heparin-tolerance test that showed a 50-minute peak. Sixteen hours later she showed slight vaginal bleeding, at which time the clotting time was 23 minutes. She was given 30 mg. of protamine sulfate in 1000 cc. of a 5 per cent solution of dextrose in water. Six hours later the clotting time was 13 minutes and all bleeding had ceased. Two days later a second pulmonary embolism occurred, whereupon heparin-gelatin-dextrose therapy was resumed for 5 additional days without further difficulty.

Comment. The bleeding in this case was unavoidable.

Case 6. H. J. (No. K6003), a 69-year-old man, underwent bilateral superficial-femoral-vein division because of pulmonary embolism after a course of heparin therapy. A heparin-tolerance test had previously shown a 40-minute peak. Forty-eight hours after operation, against the possibility of thrombosis of the profunda-femoris vein, he was started on a course of 200 mg. of heparin-gelatin-dextrose with vasoconstrictors daily. On the second day of therapy, 8 hours after the last heparin injection, at a clotting-time level of 50 minutes, the patient passed some grossly bloody urine. Heparin was stopped. The hematuria disappeared in 48 hours, but 10 days later further gross hematuria reappeared transiently. Intravenous urograms and cystoscopy revealed no evident cause for the bleeding.

Comment. This bleeding, which was probably but not necessarily due to the heparin therapy, was unavoidable.

It is well known that there is no constant relation between the tendency to bleed and the clotting-time level in the presence of heparin. Four of the bleeding patients recorded here bled at clotting-time levels usually considered within the desirable

therapeutic range, and we have seen 2 other heparinized patients who bled at clotting-time levels of thirteen and sixteen minutes, respectively. It is of interest, however, that none of the last 50 patients in this group showed a bleeding tendency. We ascribe this to a combination of three factors: generally smaller heparin dosages, heparin-tolerance testing and coincidence.

Failures of Heparin Therapy

Just as after femoral-vein division an occasional patient will suffer another pulmonary embolism that at times can be shown to arise from the ligature site, the profunda-femoris vein or the pelvic veins, even so an occasional patient will have a pulmonary embolus during or after heparin therapy. Similarly, a few patients whose signs and symptoms of venous thrombosis in the leg have completely subsided after heparin treatment will show a recurrence two days to two weeks later, at times affecting a wholly different venous channel. In this group of patients, 7 cases represent failures of therapy, inasmuch as 4 suffered further pulmonary embolism after heparin treatment and 3 other patients showed an early recurrence of a deep venous thrombosis.

Discussion

The results obtained with this heparin preparation in this group of thromboembolic cases are good, but not so good as we had hoped, in view of the 7 per cent of therapeutic failures. It is clear that the gelatin-dextrose medium makes possible a satisfactory anticoagulant effect with one injection of 200 mg. of heparin each day in the majority of patients, provided that the vasoconstrictor drugs are used in the deposit. The incidence of bleeding (8 per cent), which could probably be reduced, is not unusually high in view of the fact that 81 per cent of the patients had surgical wounds of varying recency. In selected cases the use of heparin in a gelatin-dextrose mixture in conservative doses affords a simple, convenient and effective anticoagulant method. It should not, of course, be used in patients for whom lumbar sympathetic block or surgery may soon be advisable, such as patients with iliofemoral venous thrombosis with arterial spasm. Its prolonged action makes its use unwise in treating thromboembolic disease in recently operated urologic, orthopedic, neurosurgical or thoracic patients.

Summary

The literature dealing with the various attempts to prolong the action of heparin is reviewed.

One hundred surgical cases of venous thromboembolic disease, including 31 cases of pulmonary embolism, treated solely with heparin-gelatin-dextrose are presented.

Brief case reports of 6 of the 8 patients who bled are given.

Ninety-three per cent of the patients obtained good results.

There were no fatal pulmonary emboli.

The technical assistance of Miss Gertrude Lanman and Mrs. Pauline Patch in carrying out innumerable clotting-time determinations is herewith gratefully acknowledged.

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THE HARVARD PUBLIC-HEALTH CHEST CLINIC*

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BOSTON

THE great value of x-ray examination of the chest in tuberculosis case-finding programs is beyond a doubt. Bloch and his associates[1] in 1938 stated the strong position of roentgenology: "Failure to make a diagnosis of pulmonary disease because a roentgen examination was not carried out should be regarded as negligence"; they estimated that more than 30 per cent of clinically important pulmonary disease is missed on physical examination. Photofluorography, because of its virtue of being relatively inexpensive, with no significant loss of accuracy, has made possible surveys of large numbers of persons with a minimal expenditure of funds and time; this examination has taken its place alongside routine blood counts, serology and urinalysis in a conscientious medical work-up. Ideally, x-ray study of the chest should be recommended for everyone at regular intervals, such as once a year; however, facilities and public willingness do not yet allow the ideal. Hence, efforts are being directed to groups in which one has reason to expect higher than usual yields. Such selected groups include medical students, hospital employees, gravidae, clinic patients and hospital admissions.

Hospital-admission x-ray programs have been the subject of several reports in the recent literature, and their value in discovering pulmonary disease, — tuberculosis as well as other types, — is great. Hodges, in 1934, arranged for routine chest films of 1100 patients at the Michigan University Hospital, finding significant abnormalities in 8.1 per cent.[2] A later study by the same investigator with photofluorography of 7841 patients (clinic or hospital admissions) revealed abnormalities warranting further study in 9.3 per cent[3]; survey of hospital patients yielded three times as much chest abnormality as is found in the general population. Plunkett and Mikol had chest films made in 4853 adults admitted to 14 general hospitals in 10 cities of upstate New York in 1937 and 1938, excluding known cases of tuberculosis[4]; 1.1 per cent had x-ray characteristics of clinically significant tuberculosis. Childress, Debbie and Harmon[5] surveyed by fluoroscopy or chest film 7187 patients (clinic or hospital admissions) at Grasslands Hospital, Valhalla, New York, excluding patients with clinical suspicion of pulmonary disease: 290 (4 per cent) showed manifestations of tuberculosis of which 42 (0.6 per cent) were active or questionably active; activity was subsequently established in 25 (0.35 per cent). Bloch and his associates[6] at the University of Chicago introduced routine chest fluoroscopy of patients at the Out-Patient Department of the University Clinics in 1942; films were recommended for indicated cases. Subsequent studies of abnormalities identified by this method revealed clinically important tuberculosis in 1.43 per cent of 15,000 white patients and 2.64 per cent of 25,000 Negro patients.

In 1946 one of the authors initiated steps to establish a photofluorographic unit near the Harvard Medical School for the prime purpose of obtaining serial chest studies of the professional and nonprofessional personnel of the nearby hospitals as well as of the Medical, Dental and Public Health School students. The facilities were also made available to any of the participating hospitals for surveying clinic patients. We would very much have liked to utilize the Chest Clinic as a hospital-admission x-ray program (that is, routine chest film on all admissions to the clinics or to the hospitals), but the location of the unit in a building not physically connected with any of the hospitals precluded its use for this purpose. However, in addition to the groups in which we were especially interested, — hospital personnel, medical, dental and public-health-school students and clinic patients, — registrants came to us from several schools in the vicinity as well as from several practicing physicians.

Space was obtained in the basement of the Huntington Hospital Building, now occupied by the Harvard School of Public Health. The major portion of the cost for the construction work necessary was borne by the three participating hospitals§ and the Harvard Medical School; financial aid was also given by the Massachusetts Tuberculosis and Health League, the Boston Tuberculosis Association and the Permanent Charity Fund. The Harvard School of Public Health has contributed to the office expenses. The State Department of Public Health (Division of Tuberculosis Control) provided funds for the purchase of the photofluorographic equipment as well as supplies for the operation of the unit and has also paid the salaries of its personnel. The Harvard Public Health Chest Clinic has been in continuous operation since September 29, 1947.

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Equipment and Operation

For ease of operation and reliability a 70-mm. photofluorographic machine was chosen, equipped with automatic camera and phototimer. The mechanics of the examination were simplified as much as possible. The patient is given a requisition form by the referring physician or insitution. The film is made by the secretary-technician and the roll film bearing the examinations of the preceding twenty-four hours is developed each afternoon. The interpretations are made each evening or the following morning by a radiologist of the Specialty Board level, the findings being recorded in check fashion on the original requisition form, which is then returned to the referring physician or institution. During x-ray exposure the patient is permitted to retain indoor clothing; Lewis[7] has shown that no significant detail is lost by this procedure, thus eliminating the need for dressing rooms and gowns as well as diminishing the time in performing the examination. Of course, patients are asked to remove metal objects that will obscure lung detail, such as religious medals, jewelry and fountain pens.

The radiologist may make one of four impressions or recommendations:

Negative chest.

Abnormal chest: no further x-ray study recommended. Into this category would fall lung or thoracic-cage anomalies, well calcified parenchymal or nodal lesions, mild senile emphysema or other abnormalities requiring no further radiologic investigation.

Abnormal chest: refer to x-ray department for further study. In his report the radiologist may suggest the type of further investigation, such as fluoroscopy, stereoscopic views or Bucky films. Into this category would fall all cases that could represent active tuberculosis (*Probable tuberculosis* or *Tuberculosis suspect*). Further investigation is also recommended for other findings such as abnormal cardiac silhouette and pulmonary lesions that could be of clinical significance.

Unsatisfactory films: repeat photofluorogram.

In cases in which active pulmonary tuberculosis is suggested by the photofluorogram, a follow-up form is sent to the referring physician along with the report. Answers are requested to the following questions:

After further investigation does this patient have pulmonary tuberculosis?

If so, what is its stage and activity?

Population Studied

The groups surveyed by the Harvard Chest Clinic are the following:

Harvard Medical School students are examined at six-month intervals.

The employees of the three participating hospitals, — Children's, Boston Lying-in and Peter Bent Brigham, — are surveyed at six-month intervals. This group includes nurses, intern and resident staff as well as nonprofessional employees such as ward helpers, cooks and maintenance workers.

All clinic patients at the Boston Lying-in Hospital are referred for chest examination; these are women in the early stage of pregnancy.

Peter Bent Brigham Hospital Clinic patients are sent for photofluorographic study at the discretion of the various examining physicians. All new patients are given requisitions for chest films when seen by the admitting physician. In general an attempt is made to refer old clinic patients at yearly intervals, although no definite system has been worked out to accomplish this in all cases.

Students at the Harvard School of Public Health.

A miscellaneous group consists of referrals from various practicing physicians, a neighboring small hospital, students and employees from a few schools in the vicinity.

Results

We would like to present the statistics of the Harvard Chest Clinic for a thirty-three-month period — from the opening of the unit on September 29, 1947, to July 1, 1950; results for the period after July 1, 1950, are not included since final follow-up data are not yet available for many of the more recent registrants. During this period 30,519 photofluorograms were made; inasmuch as our population includes a large number of nurses as well as clinic patients of a maternity hospital, females predominated. We examined 21,538 females (about 70 per cent of the total number) and 8981 males. Twenty-seven thousand and forty-two of the 30,519 photofluorograms (88.6 per cent) were considered normal. Of the remaining 3477 films, — interpreted as abnormal, — 513 (1.7 per cent of the total examined) suggested the possibility of active pulmonary tuberculosis. Two thousand nine hundred and sixty-four (9.7 per cent) were classified as "other abnormalities"; this group included such findings as scoliosis, abnormal cardiac outline, calcified nodes, evidences of old pleurisy and rib anomalies.

Attempts at follow-up of the important group of 513 suspected of active tuberculosis have been successful in only 454 (89 per cent) in spite of repeated letters. At present there is no foolproof machinery for assuring follow-up studies. Clinic patients on return for a repeat visit are informed of recommended further x-ray studies; unfortunately, a significant number of such patients fail to return for such a visit. A few of the physicians who refer patients to the chest clinic are negligent in making their follow-up reports. In several cases the aid of the Department of Public Health has been solicited by our unit

in obtaining adequate follow-up studies in tuberculosis suspects.

An analysis of the 454 persons whose photofluorograms suggested the possibility of tuberculosis and in whom adequate follow-up data are available yielded the following results:

Normal lungs	170 (37%)
Active pulmonary tuberculosis	72 (16%)
Inactive pulmonary tuberculosis	199 (44%)
Other abnormalities	13 (3%)

Among "other abnormalities" are included instances of sarcoidosis, atypical pneumonia, bronchiectasis and bronchitis. Thus of this group of 454, 271 (60 per cent) proved to have pulmonary tuberculosis, and only 72 were proved to be cases of active pulmonary tuberculosis.

TABLE 1. *Age and Sex Distribution of 72 Active Cases of Pulmonary Tuberculosis.*

AGE	TOTAL NO. OF CASES		MALES		FEMALES	
	no.	%	no.	%	no.	%
15–24	16	22.2	7	9.7	9	12.5
25–34	23	31.9	8	11.1	15	20.8
35–44	9	12.5	2	2.8	7	9.7
45–54	7	9.7	4	5.6	3	4.2
55–64	11	15.3	5	6.9	6	8.3
65–74	3	4.2	1	1.4	2	2.8
75 and over	3	4.2	2	2.8	1	1.4
	72	100	29	40.3	43	59.7

A significant number of photofluorograms showed calcified pulmonary scars or calcified hilar nodes. We considered these residues of tuberculosis and did not request further study; there were 667 such cases. In addition, as we have already seen, among the persons for whom further study was recommended 271 showed evidences of tuberculosis (199 inactive and 72 active), making a total of 938 with roentgenologic evidence of pulmonary tuberculosis, past or present — or 3 per cent of the 30,519 films made. Yet only 0.24 per cent of the total number surveyed were proved to have active disease.

TABLE 2. *Classification According to Stage of Disease of 72 Cases of Pulmonary Tuberculosis.*

STAGE	NO. OF PATIENTS	PERCENTAGE OF PATIENTS
Minimal	34	47
Moderately advanced	32	45
Far advanced	2	3
Unclassified	4	5

As expected from the composition of our group, most of the patients with active pulmonary tuberculosis were young; the group fifteen to thirty-five years of age contained 54 per cent of the 72 positives. The sex differential among the active cases showed no significant difference from that of the entire group: 70 per cent of all the registrants were female; 60 per cent of the 72 were female (Table 1).

DISCUSSION

From the viewpoint of tuberculosis case-finding, is the project proving worth while? In converting our findings into dollars and cents it has cost the Massachusetts Department of Public Health about $300 to discover each case of active tuberculosis. The cost for finding evidence of pulmonary tuberculosis at any stage, inactive or active, has been about $20 per case. Because of the relatively small number of persons surveyed by our unit in the face of fixed expenses (salaries and equipment), the cost per film has been high, about 68 cents. At first thought $300 may appear expensive for discovering a single active case, but in view of the high cost of hospitalization any method effecting earlier discovery will lead to a tremendous economic saving to the community, both by shortening the stay of the patient and by preventing the spread of tuberculosis to other persons. In 1950 the cost to the community in the state and county tuberculosis hospitals in Massachusetts was $78.68 per patient per week. The average patient stay was 330 days at a total cost of $3700.[8] Hence, discounting for the moment the expense to the patient or the potential patient and his family in terms of personal medical costs as well as loss in earning capacity, a method that enables the finding of persons with active pulmonary tuberculosis at the outlay of a few hundred dollars accomplishes a significant economic saving to the community.

TABLE 3. *Population Breakdown (15-Month Period).*

Total number of registrants	14,838
Clinics	6,208 (41.9%)
Patient care	5,686 (38.3%)
Miscellaneous	2,944 (19.8%)

TABLE 4. *Sources of 72 Active Cases of Tuberculosis.*

SOURCES		NO. OF CASES	PERCENTAGE
Clinics		34	47
General clinics	19		
Maternity clinic	15		
Patient care		23	32
Medical students	3		
Hospital employees	20		
General hospital	7		
Maternity hospital	7		
Children's hospital	6		
Miscellaneous		15	21
College students and employees	5		
From local physicians	10		

In addition, we believe that we are studying a very important group in which discovery of active disease is worth a high cost. The importance of finding active pulmonary tuberculosis in pregnant women is accepted by all medical authorities; our unit has uncovered 15 such cases. Infectiousness among hospital employees and medical students is

of course extremely hazardous, because of ease of transmission to debilitated patients; we found 23 such foci.

A breakdown of our 72 active cases into sources yields:

Hospital employees, professional and nonprofessional	20
Medical students	3
Maternity-clinic patients	15
General-hospital clinic patients	19
Other sources	15

A grouping of our 72 active cases according to stage of disease shows that only 47 per cent were minimal (Table 2). We have been disappointed with this, having hoped that our method of frequent resurvey would yield chiefly active cases in the early stage; we expect that as the project continues our positive cases among those being studied at regular intervals will be largely minimal, although there will still be new clinic patients with advanced disease. In any case, it appears that in our selected group tuberculosis is found in an earlier stage than in surveys of the general population in this vicinity; the recent Boston survey[9] uncovered 247 cases of active pulmonary tuberculosis; only 28 per cent were in the minimal stage.

Did any one group yield a higher dividend than the others? Our heterogeneous population may be broken down into three general groups:

Clinics — clinic patients from the Peter Bent Brigham Hospital, the Boston Lying-in Hospital and a few from the Free Hospital for Women.

Employees or persons concerned with care of patients — hospital employees (professional and nonprofessional) of the 3 participating hospitals, as well as medical students

Miscellaneous — college students and referrals from practicing physicians

In respect to such a classification, a detailed analysis of our cases according to source of referral was made for three separate periods, covering in all fifteen months. A total of 14,838 registrants were so analyzed (Table 3). Our 72 patients with active pulmonary tuberculosis were also studied according to source, again utilizing the three general divisions (Table 4). No single group shows a higher yield of positive findings than the others. The "clinics" made up 41.9 per cent of our population and contributed 47 per cent of the active cases; from the "patient care" division, comprising 38.3 per cent of the total group, gave 32 per cent of the active cases; the "miscellaneous" group made up 19.8 per cent of the total and 21 per cent of the active cases.

Analysis of the 14,838 registrants for whom we have specific data concerning source of origin shows the following incidence of active pulmonary tuberculosis computed as rate per 1000 registrants: for the "clinics" 3.22 per 1000; for the "patient-care" group 2.11 per 1000; for the "miscellaneous," 2.38 per 1000. These differences are not statistically significant.*

Summary

This is a review of the experiences at the Harvard Public Health Chest Clinic. During a thirty-three-month period 30,519 70-mm. films were made; 513 (1.5 per cent of the total) suggested active pulmonary tuberculosis and further studies were recommended. Of this group of 513, 454 have had adequate follow-up, 72 being proved to be cases of active disease (0.24 per cent of the total films taken). Forty-seven per cent of the 72 cases were shown to be minimal in extent. Among the cases have been 20 hospital employees, 15 gravidae and 3 medical students.

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CLINICAL NOTE

DRAMAMINE AS AN ADJUVANT MEASURE IN PSYCHOGENIC VOMITING*

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DRAMAMINE has been reported by various investigators to be efficacious in alleviating the nausea and vomiting of motion sickness[1] after operative procedures,[2] of aureomycin therapy,[3] after electric shock,[4] in radiation sickness[5] and in hyperemesis gravidarum.[6] Review of the literature reveals no reports on its use in psychogenic vomiting on the basis of a conversion hysteria in which no labyrinthine or other organic disease was present.

CASE REPORT

A 30-year-old unmarried man was admitted to this hospital in April, 1951, on the Neuropsychiatric Service, complaining of repeated attacks of nausea and vomiting during the previous 2 years and a weight loss of 30 pounds.

The patient dated the onset of frequent attacks of emesis to July, 1949, when he became employed as a steelworker on a construction job. The vomiting bouts occurred about twice a week without any warning and were propulsive in nature. In March, 1951, he commenced to vomit every day, often several times in a 24-hour period. This condition persisted for the next 3 weeks, at which time the patient was admitted here. At the time of admission the patient had become so weak that he was confined to bed most of the day. A close relation between his vomiting and the emotional stresses in his life was noted.

Physical examination revealed a severely cachectic man who showed evidence of marked recent weight loss. Comprehensive systemic studies revealed no organic disease. Laboratory examinations were all within normal limits. These included a complete hemogram, urinalysis, blood urea, sugar, potassium, sodium, total protein, chlorides, an electroencephalogram, electrocardiogram and chest, skull and spine x-ray films. Repeated gastrointestinal series and gastric analyses were negative. Gall-bladder visualization revealed no disease. Endocrine studies, basal metabolic rate and labyrinthine function (caloric test) were normal.

Because the vomiting had reached a dangerous level of frequency, intensive medical therapy was instituted in an attempt to control it. The patient's physical status was so poor that it was necessary to limit psychotherapy to superficial support. He was placed on several daily doses of insulin to stimulate appetite and produce a sedative effect. This was supplemented with parenteral feeding, including large doses of vitamin B complex (with pyridoxine) and adequate barbiturate sedation. After two weeks of this regimen the patient's physical status remained the same as on admission, with no relief from vomiting. It was decided at this time to withdraw the aforementioned medications and commence Dramamine, 50 mg. three times a day, as the sole medication. He had no prior knowledge about this drug at the time it was administered. After the first dose all vomiting ceased and did not recur until one week later, when the Dramamine was stopped for 36 hours. At that time the patient vomited once. When the medication was restored emesis was again controlled. Appetite improved correspondingly with the decrease in vomiting; the patient began to gain an average of 3 pounds a week. It was thought that although the vomiting had apparently been controlled by the use of this drug we had achieved merely a palliative rather than a permanent cure. Since the underlying psychopathologic etiology was still present, insight therapy was commenced, to effect a long-standing cure of the condition. Accordingly, intensive psychotherapy was commenced while the patient was still on Dramamine. After a month on this regimen, Dramamine was stopped while psychiatric treatment was continued.

A psychiatric study revealed that the patient reacted with vomiting in situations in which he was provoked to feelings of resentment toward his brother. From early life there had been marked sibling rivalry between them for maternal affection. The patient had always been jealous of his brother, who had received more attention because of illness. When the patient worked together with his brother for the first time in 1949 and was humiliated by him in front of some friends, the rivalry of earlier years was reactivated. He felt mounting resentment against his brother, which he was unable to express overtly. By the symptoms of nausea and vomiting he solved a psychologic conflict, becoming sick himself and thereby gaining more maternal attention, forcing his brother to assume more economic responsibilities and symbolically showing his hostility to him. As relations had worsened between the siblings the patient's vomiting had increased.

Psychotherapy was directed toward helping the patient to understand the connection between his emotional symptoms and physical complaints and encouraging him to verbalize his feelings so that he would no longer have to resort to vomiting. No further emesis occurred during hospitalization or after discharge.

SUMMARY

Frequently psychotherapy meets with technical difficulties in a patient who has physical complications that warrant immediate attention. A case report is presented of a patient who had vomiting of two years' duration on a psychogenic basis with a subsequent loss of 30 pounds in body weight. With the administration of Dramamine there was immediate cessation of emesis and increased appetite. The response to the drug enabled his therapist to commence intensive psychotherapy, which would have been extremely difficult and dangerous at the time he was admitted to the hospital because of his poor physical status. Response to psychiatric treatment was such that when Dramamine administration was stopped no further vomiting occurred.

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MEDICAL PROGRESS

ALLERGY TO DRUGS (Concluded)*

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FURTHER CONSIDERATION OF CERTAIN DRUGS

Urticaria due to *penicillin* has two features that deserve comment: It may subside while the drug is still being administered[147] or fail to recur on readministration,[196] or it may, on the other hand, recur in waves for a period of one to two months after administration of penicillin has been stopped.[197] It is difficult to understand why the reaction sometimes subsides despite continuation of the drug, but this paradox has been noted at times in other allergies to drugs, such as agranulocytosis. Spontaneous loss of the altered capacity, occurring after administration has stopped, is also found in other allergies to drugs. It is, of course, true that the allergic state may persist for years (it persisted at least seventeen years in one case of allergy to arsphenamine[198]), and this feature has attracted much comment in the past, but experience with Nirvanol[156, 199] many years ago showed that this was not always true. Studies with sulfonamides[129] have shown that fever may recur on readministration at a time when the skin and conjunctiva have lost their former allergy. Failure of lesions to disappear immediately after administration of the drug is stopped also occurs with other drugs and may be due to persistence of the drug in the tissues. Neither of these paradoxical features, then, is restricted to penicillin, but either one or the other seems to be unusually frequent among patients with urticaria due to penicillin.

In view of the frequency with which urticaria, and to some extent dermatitis, spontaneously fails to recur on readministration, one must be cautious in interpreting the results of deliberate attempts at desensitization.

The use of diagnostic skin tests in allergy to penicillin other than contact dermatitis has been extensively investigated.[50, 200, 201] Although patients with positive skin tests are more likely to prove allergic to penicillin than those with negative tests, the accuracy of the tests is insufficient for clinical use.

The hypothesis that sensitization by previous contact with the mold is responsible for many cases of allergy to penicillin remains unproved. It is possible that patients who promptly develop reactions on initial administration of penicillin have been sensitized by the mold. The similarity between dermatitis due to penicillin and that due to fungus infection has impressed dermatologists.[202] Sanchez-Cuenca[144] found *Penicillium* in both the sputum and the feces of a patient with a long-standing lung abscess who was suffering from urticaria due to penicillin and persisting after cessation of penicillin therapy. Attempts to answer the question by experiments using "trichophytin"[203] have not produced convincing evidence.

Lepper[204] found a higher incidence of allergy to penicillin in oil and beeswax than to crystalline penicillin in water but found no difference between the latter and procaine penicillin in oil. Antigenicity of the menstruum or increased local irritation or both caused by the penicillin in oil and beeswax were probably important factors. Patients allergic to procaine penicillin may be allergic to either the procaine[205] or the penicillin. In view of the logically expected and experimentally demonstrated[27, 206] failure of antihistaminic drugs to influence sensitization, the decreased incidence of reactions reported from "hypoallergic" preparations containing penicillin with an antihistaminic drug[207, 208] must be ascribed to suppression of manifestations of allergy to penicillin. Some patients allergic to penicillin G may tolerate penicillin O,[209] but in other patients cross reactions occur.[210]

The clinical incidence of allergy to penicillin has been estimated as 6 to 12 per cent.[211] This highly undesirable state of affairs is to a considerable extent due to the wildly indiscriminate use of penicillin on the part of many practitioners. One gathers that "aqueous penicillin" has been translated by some as "penicillin to be given out like water." However, the pressure, — and anyone dealing constantly with patients knows that it is a pressure, — exerted by a public that has become aware of the benefits but unaware of the dangers of newer drugs certainly does not make the physician's life any easier. Since repeated warnings by others have had no very gratifying results, this reviewer has no illusions that anything written here will stop the trend. On the contrary, he confidently expects the day when penicillin injections will be dispensed in drugstores by slot machines set up between the candy counter and the pinball machines. The lines forming in front of them during the season of coughs and colds will be something to see.

Streptomycin caused a 7.7 per cent incidence of contact sensitization, as tested by patch tests, in one series[212] of nurses handling it. Allergy to injected streptomycin is, of course, a serious problem

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to the tuberculous patient in need of the drug. Such a patient usually tolerates dihydrostreptomycin,[145, 213] which was introduced as a less toxic drug than streptomycin but has not fulfilled its early promise[214] and is now indicated only in patients allergic to streptomycin.

Chemotherapeutic agents have acquired a reputation as causes of skin reactions of an allergic nature, but this is not always justified. *Quinacrine* (Mepacrine, Atabrine), administered over long periods of time, has been well established as the cause of a chronic lichenoid dermatitis, "atypical lichen planus," seen frequently during World War II. Bazemore[215] readministered quinacrine to 51 patients who had subsiding chronic lichenoid dermatitis from previous quinacrine administration. Five developed an acute dermatitis, dissimilar to their lichenoid dermatitis and unassociated with exacerbation of their healing lichenoid lesions, during the first week of readministration. Daily administration of 200 mg. of quinacrine hydrochloride was continued in the others for two to three months. Nine of the patients developed new lichenoid lesions, with exacerbation of their old lesions. The earliest this occurred was twenty-three days after readministration was begun. This is not characteristic of allergic dermatitis. Clarke,[216] however, reported prompt exacerbation of chronic lichenoid dermatitis on readministration of quinacrine to a patient whose lesions were in a "static" state.

Iodine causes at least three different types of reactions. Direct chemical burns, such as those following ingestion of the tincture of iodine, need no further comment. Generalized dermatitis following the localized external use of small amounts of elemental iodine has been shown to be an acquired specific hypersensitivity, an allergy, in some patients.[57] Other reactions consistent with allergy to drugs, such as urticaria[57] and thrombocytopenic purpura,[112] may occur with the dermatitis. The changed antigenicity of iodinated proteins was demonstrated many years ago.[14] Dermatitis and coryza, "iodism," following the ingestion of the iodide ion is more obscure in nature. One case in which a patient apparently acquired sensitivity to a dose of potassium iodide formerly tolerated is noted in Table 2, but the report is brief and not entirely convincing. The previously noted case of thrombocytopenic purpura due to potassium iodide shows that one can become allergic to ingested iodide ion. It may seem difficult to conceive of sensitizing exposure to an anion that is a normal constituent of extracellular fluid and a normal component of most diets, but the factor of dose must be considered. Large doses of iodide by mouth may increase the serum protein-bound iodine[217]; neither the exact nature of this complex nor the mechanism of its formation is clear, but its antigenicity is at least a possibility. Seymour,[57] reviewing 13 cases of presumably allergic dermatitis due to external use of elemental iodine, found that 5 patients had evidence of concomitant mucous-membrane "iodism." The differences, — not necessarily acquired, — in individual sensitivity to ingested iodide ion have impressed many. Wile[218] explored a dose range of 0.3 to 13 gm. per day administered for weeks and stated: "We found that a large number of patients would take relatively enormous doses of iodide without the slightest sign of a pustule, and we were able to establish, moreover, that when a tendency to pustulation occurred, it apparently bore no relation to the amount of drug ingested." The lack of obvious relation between dose and response is significant. Studies on the relation of the skin lesions caused by the bromide ion to the blood bromide concentration have given contradictory results,[219, 220] but Sherman and Arieff,[221] who gave the most convincing protocols, found no apparent correlation. In summary, the skin and mucous-membrane lesions caused by iodide and bromide ingestion appear to be highly dependent on individual sensitivity but are not necessarily allergic.

Iodopyracet (Diodrast) injection may cause severe and even fatal reactions that resemble anaphylaxis and may be accompanied by urticaria.[222] In many cases patients in whom these reactions occur have no history of previous exposure to the drug. There is seldom a history of previous reactions to iodine, although it is possible that cross sensitivity occasionally exists.[223]

Local anesthetics have several characteristics of clinical and experimental importance in allergy: They are effective sensitizing agents in common use; they produce contact dermatitis, which is easy to study; and they are closely interrelated chemically. Studies of cross reactions to local anesthetics in man[185, 224, 225] have shown that patients become sensitized to part of the molecule; that is, they cross-react to compounds sharing certain structural features with the sensitizing compound but not to compounds sharing others. The pattern of cross sensitization is not the same in all patients; it is as if different patients became allergic to different parts of the molecule. In general application one might expect this principle to be most important for complicated molecules differing only slightly. It is thus unlikely that every patient who is allergic to streptomycin will tolerate dihydrostreptomycin. Studies with butyl aminobenzoate (Butesin)[168] have shown at least one case in which the cross reaction to a compound to which the patient had very probably never been exposed was greater than the reaction to the sensitizing drug, butyl aminobenzoate.

Vitamin B_{12} may be mentioned as an example of the advantage of obtaining in pure form the active ingredient of a mixture. Patients allergic to liver extract have been found to tolerate Vitamin B_{12}.[226, 227]

Finally, the *antihistaminic drugs* illustrate the important fact that drugs used in the treatment of allergy may themselves sensitize the patient. For example, Thephorin ointment caused contact sensitization in 2.4 per cent of 1343 patients.[228]

It is apparent that the "peripheral" approach to allergy stressed here, — that is, one that avoids the central issue, the demonstration of antibodies, — is often inconclusive. Because of the failure of passive transfer in most allergies to drugs, the results of such attempts have been largely ignored in this review. However, passive transfer, by means of serum or blister fluid, has occasionally been accomplished in human allergy to drugs,[229] and the previously mentioned cellular technic used in animals offers further promise. The development of a reliable and generally applicable method would be a most helpful advance.

Diagnosis

Although patch tests in contact dermatitis do not perfectly reproduce clinical conditions, they approximate readministration and are therefore valuable in the diagnosis of this reaction. However, patch tests occasionally cause local reactions severe and persistent enough to be distressing. Patients not allergic to the drug in question may, ironically, be sensitized by the test itself. In other allergies to drugs, including other types of dermatitis, skin tests are generally unreliable.[27, 38, 50, 127, 200, 201, 230] The common and reasonable explanation is that we use the hapten as antigen, whereas the patient is allergic to some as yet unknown conjugate. A further drawback is that the physician occasionally obtains a true positive test that is more positive than he bargained for, the patient developing an alarming systemic reaction. Leftwich[231] used the serum of normal patients given full doses of sulfonamides as skin-testing antigen in patients allergic to sulfonamides. Dameshek and Colmes[80] used serum that had been mixed in vitro with aminopyrine as skin-testing antigen in patients allergic to aminopyrine. Other investigators have not been able to confirm their reported successes.[232]

Diagnosis, then, must usually rest on history, observation of the results of stopping the suspected drug and, at times, readministration by the same route as originally used. Absence of a history of sensitizing exposure means nothing; such exposure may have been unnoticed, forgotten, or even nonexistent, since one may be dealing with a cross reaction. Even the eliciting exposure may be denied. Furthermore, it is well to remember that a patient may tolerate a drug for many years before suddenly becoming allergic to it. Nevertheless, a positive history is usually easier to obtain in allergy to drugs than in other types of allergy. Although the labeling of medicines is far from perfect, it is easier to ascertain the drugs a patient has taken than to determine what dyes he has touched in wearing his clothes or what materials he has inhaled while walking around.

Stopping the responsible drug usually (though not invariably) is followed by subsidence or at least improvement of the reaction within a few days and is a useful diagnostic and therapeutic procedure. However, there may be pressing reasons for continuing a suspected drug, and allergy to nonprotein drugs seldom, if ever, directly diminishes pharmacologic actions. One may divide the reactions into two classes, the immediately dangerous and the potentially dangerous. Angioneurotic edema, asthma, bone-marrow depression, exfoliative dermatitis, liver damage and evidence of periarteritis nodosa are immediately dangerous and demand immediate stopping of suspected drugs. Although the reaction may occasionally subside despite continued administration of the offending drug,[233] such therapeutic acrobatics probably increase the risk and are not justified. Even though a single drug may be the principal suspect, one should, whenever possible, stop all drugs that the patient is taking and give only those drugs necessary to control the reaction itself, as, for instance, chemotherapy in agranulocytosis or exfoliative dermatitis. If one must substitute another drug for one that has been discontinued, a chemically unrelated drug should be chosen whenever possible.

Reactions other than those listed above are usually not immediately dangerous but are always potentially so. Thus, a relatively innocent dermatitis may progress to exfoliation, particularly if the responsible drug is continued,[57, 62] and a more wretched condition than advanced exfoliative dermatitis is difficult to imagine. One must therefore weigh the advantages of continuing the drug against the present discomfort and possible future danger to the patient. It is usually wise to stop the drug.

The reaction having subsided, the question of testing by systemic readministration arises. It must be realized that this review has stressed the positive side of the story. For most of the drugs and reactions discussed there are other reports of apparently identical situations in which readministration failed to elicit a recurrence. But the important question is, after all, not "What happened to the patient?" but "What will happen if he again receives this drug for some future indication?" Recurrence on readministration now does not inevitably condemn him to the same result in the future, but it indicates a great risk and is far more significant than a positive skin test. Therefore controlled systemic readministration of a small dose, producing a safe but diagnostic reaction in miniature, — so-called "cautious readministration," — seems logical. However, if skin tests, which do not attempt to reproduce the original reaction, occasionally lead to severe systemic reactions, deliberate attempts to reproduce the reaction in miniature certainly carry danger. At this point one comes upon one of the

most abrupt dead ends in allergy. The relation of dose to response in allergy to systemically administered drugs is so obscure that it is very difficult to make a reasonable estimate of the indicated dose in such a test. Coulson and Stevens[234, 235] have studied the dose-response curves for protein anaphylaxis in guinea pigs, and Becker[236] has studied the same function in skin tests with ragweed in a selected population, but investigation using simple chemical compounds is desirable. Lepper[204] found the incidence of allergic reactions to aqueous penicillin to be 0.6 per cent in patients receiving up to 6,000,000 units daily but 7.8 per cent in 51 receiving more than this amount. Van Winkle[192] found no difference in the incidence of fever and agranulocytosis from thiouracil whether the daily dose was 100 mg. or 1 gm. At present the physician cannot be blamed if he is wary of the serious reactions that may promptly follow "small" doses and leaves the diagnosis unconfirmed in many instances. If testing by readministration is performed and a diagnosis of allergy is made, the information should not be wasted. The patient should be informed of the fact and told to report it in advance to any physician treating him in the future. He should also be given a written statement. Although there are, unfortunately, "doctor-proof" patients who cannot follow even the simplest advice about their own health, the majority will remember. Often the reactions themselves are not easily forgotten.

Prevention

These are four aspects of prevention: detection in advance of patients allergic to drugs; early diagnosis of mild reactions before they progress to severe ones; prevention of reactions despite administration of the drugs that would be expected to cause them; and development of new drugs that will be very weak sensitizing agents. The first has already been discussed.

An example of the second aspect of prevention is the attempt to decrease the incidence of agranulocytosis during thiouracil or sulfonamide administration by repeated white-cell counts. Van Winkle[192] showed that patients found to have leukopenia (that is, white-cell counts below 4000 per cu. mm.) without other evidence of agranulocytosis during thiouracil treatment were more likely to develop agranulocytosis than those with normal counts. However, Young[237] was unable to find any evidence in the literature that serial counts had actually decreased the incidence of agranulocytosis from sulfonamides. Unless one assumes that agranulocytosis is an all-or-none reaction, totally uninfluenced by stopping the drug once the count begins to fall, it follows from Van Winkle's report that repeated counts would be certain to do some good in a large enough series of cases. It remains to be demonstrated, however, that any schedule of blood counts usable in practice makes a difference sufficient to justify the inconvenience and expense to patients, particularly those not in a hospital.

The problem of preventing reactions despite administration of the responsible drug has been approached in several ways. As one would expect, para-aminobenzoic acid, even in doses that abolished the therapeutic effectiveness of sulfathiazole, failed to prevent dermatitis and fever when sulfathiazole was administered to patients allergic to the latter drug.[238] In Pillsbury's series,[196] the concomitant administration of an antihistaminic drug definitely appeared to abolish urticaria due to penicillin in one case cited as an example by the authors; it is not clear whether concomitant administration was tried in other cases in this series. Attempts to desensitize patients allergic to simple chemical compounds, using the methods familiar in allergy to proteins, have not had very convincing success.[18] Efforts to prevent sensitization in man have also been disappointing. White and Baer[239] used preliminary application of subsensitizing concentrations of dinitrochlorobenzene in an unsuccessful attempt to prevent sensitization from subsequent application of higher concentrations. Grolnick[240] tried, by preliminary feeding of Krameria, to decrease the incidence of allergic reactions due to Krameria applied to the skin. This experiment was unsuccessful, although Chase[241] had previously shown a decreased incidence of sensitization from intracutaneously injected dinitrochlorobenzene in rats previously fed the compound. Concomitant administration of folic acid failed to prevent agranulocytosis from thiouracil in a patient of Newman and Jones.[242]

It is apparent from the previous discussion of dose-response relation that decreasing the dose of a drug to some lower but still clinically useful amount is not likely to be helpful in allergy to drugs, although such a change in dosage may succeed in abolishing nonallergic reactions to drugs. The studies of Plummer and Wheeler[243] on reactions to sulfadiazine illustrate this point well. There was a striking difference in the incidence of renal damage between patients receiving 6 gm. daily and those receiving 3 gm. daily. This difference in dose did not appear to influence the incidence of "drug fever."

The development of new drugs that will produce a very low incidence of sensitization is probably the most important aspect of prevention. Allergy to drugs is the one form of allergy in which the physician controls, to a considerable degree, the exposure of the patient. The prevention of agranulocytosis from aminopyrine, for example, has been highly effective; the drug has been largely abandoned in favor of safer substitutes.

Predicting, on the basis of animal tests, the capacity of a new drug to sensitize human beings may be of practical interest in the future, but at present physicians must concern themselves with the results obtained in man. Ability to sensitize the skin by contact may be studied by "prophetic patch

tests" similar to those used in industry[244] to evaluate dyes used in clothing. Human volunteers are given two exposures separated by a suitable incubation period. However, such patch tests do not perfectly reproduce clinical conditions, and an adequate evaluation is not always obtained.[245, 246] In general the results of actual clinical trials are the only useful criteria if a new drug is proposed as a substitute for one already in use. However, very little attention can be paid to the mere statement that no allergy has been found in a "large" series of patients treated with the new drug. Drugs that sensitize the majority of patients, as Nirvanol did in children, are seldom used clinically. In practice, allergy to drugs is a problem of the minority, and it requires a surprisingly large series of patients to substantiate the statement that a new drug is better than one in use, when the incidence of allergy to the latter is already low. In a series of 1130 patients treated with propylthiouracil 7 cases of agranulocytosis were reported.[247] Calculation by the method of Chi-square shows that any new drug proposed as a substitute for propylthiouracil and causing no agranulocytosis at all would have to be used in 882 cases before one could state that there was a 95-out-of-100 probability that the difference was not due to chance. A questionnaire survey of "sensitivity" to aspirin showed 281 cases out of approximately 88,000 patients seen by practicing allergists.[248] (The crude data given by the authors have been used, but their corrections have been slightly modified.) Approximately 1500 patients taken from allergists' practice would be the minimum number in which a new drug could be shown to be superior by the aforementioned standards. Epstein,[249] discussing antihistaminic drugs, commented: "When we reported our results with thenylpyramine cream, we stated that so far we had not seen a case of sensitization. But the printer's ink was hardly dry on our paper before we saw the first case of contact dermatitis from this cream."

Treatment

Treatment of allergy to drugs may be considered in four sections.

Immediate relief of serious allergic reactions to drugs requires in general the same emergency measures, such as sympathomimetic amines, aminophylline and mechanical relief of obstruction of the airways, as similar reactions from other causes. Most studies of antihistaminic drugs have been concerned with the value of one drug as opposed to another, or the value of these drugs in one type of reaction as opposed to another type; the value of antihistaminic drugs in allergic reactions to drugs as opposed to other antigens cannot be stated. The use of antihistaminic drugs in the treatment of anaphylactic shock is rational and has been credited with saving at least one patient.[250] Antihistaminic drugs appear to be often but not invariably useful in urticaria and angioneurotic edema, often but not invariably disappointing in contact dermatitis and the serum-sickness syndrome and of little use in asthma.[196, 251-254] When a rapid effect is urgently needed, intravenous injection of 10–50 mg. of diphenhydramine hydrochloride (Benadryl) over a period of a few minutes is advisable, but a patient in need of such urgent treatment should also be given all other indicated medications — especially vasoconstrictor drugs if there is dangerous edema.

Prevention of dangerous secondary complications should be promptly considered. The use of vigorous prophylactic chemotherapy in agranulocytosis is an outstanding example. Patients have recovered after granulocytes had been completely absent from the peripheral blood for as long as a week,[255] and the prevention of infection during this time is crucial.

The desirability of withdrawing the offending drug in most cases has been previously discussed.

Most allergic reactions to drugs will respond to the management described above. *Severe persistent* reactions are usually indications for ACTH or cortisone.[256] Reactions to drugs in which benefit has been reported are dermatitis,[257-259] including the exfoliative type,[257, 258] keratitis,[257] urticaria,[257, 258] angioneurotic edema,[257] the serum-sickness syndrome,[257] asthma[257] and agranulocytosis.[260] The impression is gained that many physicians are becoming disillusioned with regard to these hormones because they are expensive and sometimes difficult to obtain, have disturbing side-effects and usually benefit the patient only while he is receiving them. Severe persistent allergic reactions to drugs occur only in a small minority of patients, justify the risk of side-effects from ACTH or cortisone and, — most important of all,— represent a temporary situation, since the cause can be removed; thus a temporary effect is all that is asked of ACTH or cortisone. This is therefore one of the most rational and promising indications for ACTH or cortisone.

The role of vitamin C in the treatment of allergy to drugs has aroused the interest of some workers, among whom the writer is not included. Dimercaprol (BAL) has been found to accelerate recovery from exfoliative dermatitis due to arsenical drugs.[261, 262]

Conclusion

A discussion of this subject written three hundred years from now will perhaps include a brief historic review of the present time. It is possible that the hypothetical author will say: "By the middle of the twentieth century allergy to drugs had become a problem of some importance. Rapid advances in therapeutics had made many new sensitizing agents available to physicians, and the temptation to use them promiscuously was great. Precise diagnosis in this field was often difficult. Suitable technics for passive transfer were not available, and the re-

lation of dose to response was still obscure. On the other hand, a large amount of information concerning the fundamental mechanism of allergy to drugs had accumulated; those who were concerned with the development of new drugs had come to realize that sensitizing capacity was an important property; and the prognosis in even the most severe types of reactions had been strikingly improved by the introduction of ACTH and cortisone." There is at least reason to expect that such a review will not begin: "The twentieth century must have been the nadir of therapeutics. . . ."

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 37501

PRESENTATION OF CASE

First admission. A fifty-year-old man was admitted to the hospital because of progressive swelling of the ankles and abdomen.

Twenty months before entry the patient noted the onset of dyspnea on slight exertion. He was examined by a physician, who prescribed digitalis, 0.1 gm. daily. Six months before entry he noticed swelling of the ankles and legs and an increase in the dyspnea. The swelling progressed slowly to include the abdomen and scrotum. In spite of treatment with digitalis, Mercuhydrin and ammonium chloride, the symptoms progressed. The patient had no chest pain or cyanosis, and he had been able to sleep flat in bed on one pillow almost every night.

Thirty-one years before admission the patient had had gonorrhea and two years later a penile sore, for which treatment was advised but refused. Twenty-five years prior to entry sore white patches appeared on the tongue and persisted during the subsequent years. Seven years before admission a scrotal rash appeared, a positive "blood test" was found and two courses of Mapharsen treatment were completed. No other abnormality was noted. Two years prior to entry he received 6,600,000 units of penicillin and after this was told that the "blood test" was negative. There was no history of rheumatic fever or chorea. There was a history of a heavy alcoholic intake for many years.

Physical examination revealed an obese and dyspneic man. There was no cyanosis. The left pupil was irregular and did not react; the right pupil was normal. The tongue showed severe generalized leukoplakia. The neck and temporal veins were distended in the sitting position. A few scattered moist rales were heard at the left lung base. The heart was enlarged to the left anterior axillary line. There was a grossly irregular rhythm. The mitral first sound was absent and a third sound was heard in the fourth left intercostal space. At the apex there was a Grade II systolic murmur and a low-pitched diastolic rumble. At the base a Grade II high-pitched diastolic blowing murmur was heard along the left sternal border. There were no capillary pulsations, but the pulses were bounding. The abdomen was distended with a demonstrable fluid wave. A nontender liver was felt 11 cm. below the right costal margin. There was + pitting edema of the abdominal wall and the genitalia and +++ pitting edema of the legs.

The temperature was 100°F., the pulse 100 and the respirations 20. The blood pressure was 140 systolic, 35 diastolic.

The urine had a specific gravity of 1.022 and gave a + albumin reaction. Examination of the blood showed a white-cell count of 7500 with a normal differential and a hemoglobin of 12 gm. The nonprotein nitrogen was 50 mg., the total protein 5.34 gm., with an albumin-globulin ratio of 2.1, and the fasting blood sugar 80 mg. per 100 cc.; the carbon-dioxide combining power was 24.8 milliequiv., the sodium 134.2 milliequiv. and the chlorides 101 milliequiv. per liter. The prothrombin time was 26 seconds (normal, 17 seconds), and the cephalin-flocculation test was negative. A blood Hinton reaction was + in the undiluted sample; a blood Kahn reaction was ++++ in the undiluted and ++ in the 1:2 dilution. Spinal-fluid Wassermann and Hinton reactions were negative. The colloidal gold curve of the spinal fluid was 0011100000. An x-ray film of the chest showed moderate prominence of the pulmonary vessels and engorgement of the lung roots. The heart was greatly enlarged, with a transverse diameter of 23 cm.; this was maximal on the left, but both ventricles were enlarged. The aorta was elongated and widened, but no calcification was noted (Fig. 1). An electrocardiogram showed auricular fibrillation with a ventricular rate of 100, a QRS interval of 0.08 second, and left-axis deviation. The T waves were upright in Leads 2, 3, AVF and V_4, diphasic in Leads 1, AVL, V_5 and V_6 and inverted in Leads V_1, V_2, and V_3.

Paracentesis, with the removal of 11.5 liters of fluid with a specific gravity of 1.015, resulted in a weight loss of twenty-three pounds. Cytologic studies on the fluid were negative for tumor cells. The patient was placed on a moderately low sodium diet and given intramuscular injections of Mercuhydrin and digitalis. His pulse varied between 80 and 100; his weight dropped from 122 kg. to 81.9 kg. with continued diuresis. On the ninth day a repeat electrocardiogram showed auricular fibrillation at a rate of 90 but no other significant change. He was discharged after 18 days on restricted activity and a medical regimen similar to that which he had received in the hospital. Prior to discharge the nonprotein nitrogen was 25 mg. per 100 cc. and the serum sodium 133 milliequiv. per liter. The dyspnea

was much improved, but although significant diuresis had ceased several days previously there was still ++ pitting edema of the legs.

Second admission (14 months later). The patient was readmitted because of an ulcer on the tongue. After discharge he had felt reasonably well for a short period, but the dyspnea again became more severe and his abdomen again increased in size, with considerable weight gain. Twelve months before entry a paracentesis was performed, with the removal of 7800 cc. of fluid. Following this,

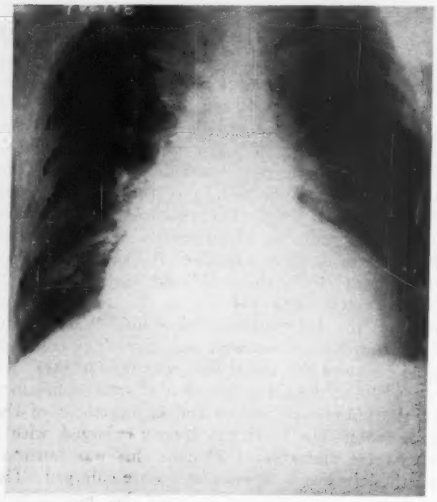

FIGURE I.

intravenous injection of Mercuhydrin resulted in a good diuresis, and he began to improve generally. Auricular fibrillation continued, but his weight fell, dyspnea decreased, leg edema was only slight in the evening and the liver decreased markedly in size. Nine months before admission the patient was able to return to light work. For the four months prior to admission no Mercuhydrin had been necessary. He had been able to carry out light activity quite well, with only some tightness in the chest on walking, which was relieved by rest. About eight weeks before admission he developed a painful persistent ulceration on the right side of the tongue in an area of leukoplakia. A biopsy of this showed Grade II squamous-cell carcinoma.

Physical examination showed an ulcerated 3-cm. elevated lesion on the right lateral border of the tongue, almost at the base. The neck veins were distended to the angle of the jaw with the patient in the sitting position but did not pulsate. The point of maximal cardiac impulse was in the sixth intercostal space at the anterior axillary line. Cardiac murmurs were unchanged from the first admission. There were a few rales at both lung bases. The liver could be palpated a handbreadth below the costal margin. It was firm, smooth and nontender. There was + pitting edema of the lower extremities. A Durozíez murmur was heard.

The temperature was 98°F., the pulse 80 and grossly irregular and the respirations 18. The blood pressure was 155 systolic, 55 diastolic.

Urinalysis was negative. Examination of the blood showed a white-cell count of 5500 per cu. mm. and a hemoglobin of 13 gm. The nonprotein nitrogen was 17 mg., the total protein 7.12 gm., with an albumin-globulin ratio of 2, and the alkaline phosphatase 12.7 units per 100 cc. The cephalin-flocculation test was negative. Bromsulfalein determination showed 12 per cent retention of the dye. An x-ray film of the chest showed no significant change. Fluoroscopic examination of the chest showed an area suggestive of calcification in the region of the aortic valve, and the aorta showed rapid diastolic return to resting position. An electrocardiogram showed auricular fibrillation at a rate of 75, a QRS interval of 0.08 second, normal voltage and left-axis deviation. The ST segment was sagging in Leads 1, AVL, V_4 and V_6. The T waves were diphasic in Leads 1, AVL, V_4, V_5 and V_6.

The patient received Mercuhydrin, digitalis and ammonium chloride. Excision by electrocoagulation of the lesion on the tongue was planned. On the sixth day, during intubation under pentothal sodium prior to operation, his heart suddenly stopped beating. Vigorous resuscitation methods, including cardiac massage, were of no avail.

DIFFERENTIAL DIAGNOSIS

DR. HOWARD B. SPRAGUE*: This fifty-one-year-old man died in three years from the onset of congestive symptoms. It seems to me that one double diagnosis I can be reasonably sure of is syphilis and chronic alcoholism. It reminds me of what Dr. C. Morton Smith used to quote years ago: "How appropriate it is that the spirochete of syphilis takes the form of a corkscrew." That, of course, was prior to the modern streamlined method of opening a bottle of whisky. I think that this man was a rather debonair fellow, because he worried very little about his venereal disease; against all advice and in spite of a persistently sore mouth he went untreated for 24 years after the infection and then had only two courses of arsenic and one of penicillin. However, it is one thing to diagnose syphilis and another to try to explain the degree of visceral damage. A primary infection untreated for twenty-

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four years provides an ideal background for syphilitic cardiovascular involvement. It seems as if the main question is: Was there involvement of the heart, the aorta and the liver? The illness started with dyspnea, followed by edema of the ankles, legs, belly and scrotum and by ascites, but orthopnea was not a prominent symptom; in fact, the picture looks more like right than left heart failure.

Let me consider the liver first. I would say it had been grossly insulted. Cardiac patients, it seems to me, nowadays rarely develop ascites requiring tapping to the amounts of 11,500 and 7800 cc. This can occur with constrictive pericarditis. I think this must mean more than simple cardiac failure and cardiac cirrhosis. Presumably there is the element associated with alcoholism, and perhaps syphilis. The liver was said to be smooth and nontender, which is against simple congestive failure's being the entire picture. The patient may not have felt pain too readily. There was no jaundice. Of course, metastatic cancer may give a clinically smooth liver. This man was obese; perhaps it was difficult to palpate the abdomen, but after tapping I should imagine the physicians had a good idea of what the liver felt like. I cannot rule out a secondary cancer as a complication, — a hepatoma, — but it does not seem to me that the course of the man's illness was very consistent with malignancy. It was pointed out years ago that gumma of the liver may go with leukoplakia of the tongue,[1] but a gummatous liver should be a knobby liver. I do not think we have the opportunity of palpating many syphilitic livers nowadays, and there are clinical exceptions to a knobby liver in syphilis. I believe even the diffuse cirrhotic change sometimes causes an irregular liver. Amyloid disease does not usually lead to ascites or jaundice; no Congo red test was done in this case.

The laboratory tests do not mean a great deal to me. The albumin-globulin ratio was normal, the total protein was low and later normal. The prothrombin time was somewhat rapid, but it seems of little significance. The bromsulfalein retention was not remarkable in view of the heart failure. A negative cephalin-flocculation test may be common in primary or secondary malignancy of the liver but it is less likely in cirrhosis, although it seems to me the latter is not very consistent. The alkaline phosphatase is in the range consistent with cirrhosis. Guttman and Hanger[2] reported ten years ago 9 cases of congestive failure in which the alkaline phosphatase was never over 10 units and the cephalin-flocculation tests were all negative except in subacute bacterial endocarditis. In cirrhosis there were twice as many giving strongly positive cephalin-flocculation tests as negative — and again there is an inconsistency in the literature, because Cantarow and Trumper[3] report that the cephalin-flocculation test is positive in the majority of cases of cirrhosis and chronic passive congestion and in certain cases of malignancy. The tests show that this patient had something wrong with his liver, and I shall be interested to find out what Dr. Castleman found in it.

As for the heart, the syphilitic patient with aortic regurgitation, which I would say this man had, has aortitis unless it is disproved. Is experience a good teacher? I hesitate to be sure of that in relation to these clinicopathological meetings. I think we ought to try to forget every probability and reach out into the air. Anyway, nine years ago I published a paper[4] in which I reported the analysis of 5044 autopsies from this hospital between the years of 1925 and 1940 in an attempt to find typical syphilitic aortitis with aortic regurgitation. I could find only 22 cases of that sort that had positive serology, electrocardiographic studies and complete autopsy findings. I said at that time — I mention it now to cover myself: "There is perhaps no cardiovascular condition in which more surprises at the autopsy table may appear." In fact, it was difficult to find an uncomplicated case of syphilitic aortitis at the Massachusetts General Hospital. Rheumatic heart disease was found combined with it, as were congenital heart disease, bacterial endocarditis, ruptured aortic cusps, aneurysm, rupture into the pulmonary artery, hypertension and in one case syphilitic, congenital and rheumatic heart disease and subacute bacterial endocarditis all together. Aortic regurgitation, I found, could occur from fusiform dilatation of the aorta without evidence of separation of the commissures at autopsy. Finally the microscopical picture not infrequently had to be invoked to settle the diagnosis of the disease in the root of the aorta.

May we have your opinion of the x-ray films in this case, Dr. Wyman?

Dr. Stanley M. Wyman: The heart shadow as recorded is tremendously enlarged. The enlargement appears to be predominantly left ventricular, but I think there must be a considerable degree of enlargement of the right ventricle and probably of the auricles as well. The main pulmonary artery and hilar and pulmonary vascular vessels are all engorged. The azygos vein is unusually well seen; the enlarged superior vena cava forms the right mediastinal border, extending quite far laterally (Fig. 1). There is some change, I believe, in the second examination, chiefly manifested by increased prominence of the pulmonary-vessel shadow with some fluid now in the pleural spaces, evidence of more congestive change. The aorta, in which I think we are primarily interested, does not seem as prominent in the ascending portion as one might expect to find it.

Dr. Sprague: It has no calcification in it?

Dr. Wyman: No; I looked particularly for that.

Dr. Sprague: What was meant by the suggestion of calcification in the region of the aortic valve?

DR. WYMAN: I can pass no judgment on that. It was observed by one physician fluoroscopically. I cannot make any comment from the films.

DR. SPRAGUE: The x-ray films show that the heart appeared enlarged in all the chambers; there is evidence of congestive failure, but it fails to reveal the supposedly specific calcification of the ascending portion of the aorta that is seen with syphilis. In this case the features inconsistent with simple syphilitic aortitis or aortic regurgitation are the auricular fibrillation, the enlargement of both ventricles, the suggestive calcification of the aortic valve and perhaps the diastolic murmur at the apex, which may have been due to the Austin–Flint mechanism. These things inclined me to a diagnosis of syphilitic aortitis combined with old healed lesions of the mitral and aortic valves of a rheumatic origin. Any additional complexities would be shots in the dark. I suspect that the sudden death was due to syphilitic involvement of the coronary ostia. So I shall come out with syphilitic aortitis, — hoping it will be found at least microscopically, — aortic regurgitation, old rheumatic heart disease and cirrhosis of "alcoholic" and cardiac types.

DR. ERNEST CRAIGE: This patient was seen on several occasions at Cardiac Rounds; the opinions were divided between rheumatic and syphilitic heart disease. The final opinion of the group was that he had both rheumatic and syphilitic heart disease. No other diagnosis was seriously considered. The absence of aortic stenosis was thought to be somewhat against a single diagnosis of rheumatic heart disease, because he should have developed some stenosis after so many years. Also somewhat against it was the fact that he had passed a physical examination at a factory near here seven years ago; at that time the heart was said to be normal, which would be inconsistent with his having had long-standing rheumatic heart disease.

DR. SPRAGUE: My notes say that I do not mean mitral stenosis but at least mitral regurgitation with thickening of the cusps.

CLINICAL DIAGNOSIS

Syphilitic and rheumatic heart disease.

DR. SPRAGUE'S DIAGNOSES

Syphilitic and rheumatic heart disease with aortic regurgitation.
Cirrhosis, alcoholic and cardiac.

ANATOMICAL DIAGNOSES

Marked fenestration of aortic cusps leading to aortic regurgitation.
Cardiac hypertrophy and dilatation, marked (950 gm.).
Syphilitic aortitis, mild.
Portal cirrhosis of liver.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: Dr. Sprague is one of the few persons to whom I would dare to give this case to discuss, because he so enjoys the exotic conditions of the cardiovascular system. Since we had not seen one like it before, we did not expect him to make the diagnosis.

The heart at autopsy was tremendous in size, weighed 950 gm. and showed hypertrophy and marked dilatation of the left side of the heart such as one would expect with long-standing aortic regurgitation. The aorta itself showed in the gross nothing that we could be sure was evidence of a syphilitic aortitis — just a moderate degree of intimal wrinkling of the descending portion. There was no involvement of the ascending aorta and no separation of the cusps at their commissures, so that we were quite certain that the aortic insufficiency was not due to syphilitic involvement of the aorta in the region of the aortic valve, nor was there any narrowing of the coronary mouths such as you often see in syphilitic aortitis. The marked flattening of the trabeculae carneae of the left ventricle was good evidence that aortic regurgitation had been present, and this picture demonstrates its etiology (Fig. 2). The aortic cusps are full of holes. Holes or fenestrations are often seen in aortic cusps normally; they are located usually near the free edge of the cusp and do not go down very far into the body of the cusps. Thus when the valve closes the fenestrations are above the line of closure, so that the only communication is between cusps above the line of closure within the sinuses of Valsalva and therefore the fenestrations do not lead to any aortic regurgitation. In this case, however, the extensive fenestration involving all three cusps extends down below the line of closure, thus allowing for free regurgitation. I have never seen fenestration to this degree before, and in the absence of

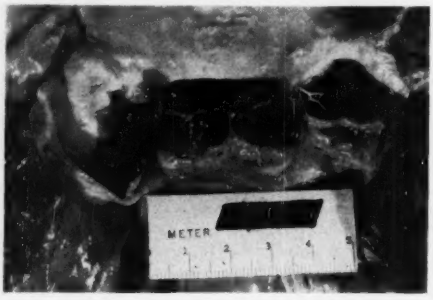

FIGURE 2. *Aortic Valve, Showing Marked Fenestration. Black paper has been inserted in sinuses of Valsalva to accentuate the fenestrations. Note severe atherosclerosis and absence of any syphilitic change in the ascending aorta.*

any other cause for the aortic insufficiency I must assume it was due to this extensive fenestration. Similar but not so extensive changes were present in the pulmonary valve. The microscopical sections of the cusps show extensive mucinous degeneration of the cusps between the two layers of endothelium. We always see some degeneration in anyone over thirty, but not to this extent; what has happened is that the cusp itself has degenerated. There is very little known about fenestration of the aortic valves. The only comparatively recent paper that I know of is by Fox,[5] who over 20 years ago found, in an examination of about 400 hearts, that 80 per cent had some degree of fenestration. He noted that the number of fenestrations increased as the patients grew older, which would be much more in favor of this being an acquired condition rather than a congenital lesion, which is sort of taken for granted. Fenestrations are not seen in infants or in children, but they are seen frequently in older people. This mucinous type of degeneration is similar to what one sees in the aorta itself in older persons and is believed to be related to medionecrosis aortica cystica, which is the most common precursor of dissecting aneurysms.[6]

The liver was enlarged, weighing 2800 gm., and showed a mild degree of cirrhosis, which I believe was on an alcoholic basis. We were unable to find the exact cause of death. It was just a cardiac standstill during the anesthesia induction.

DR. ALFRED KRANES: The mitral valve was perfectly normal?

DR. CASTLEMAN: Yes.

DR. SPRAGUE: The microscopical sections of the aorta were perfectly normal?

DR. CASTLEMAN: No; they showed a mild degree of syphilitic aortitis. It was very mild and I do not believe it had anything to do with the aortic insufficiency.

DR. SPRAGUE: I appreciate the honor of having this case in the same way that the bull appreciates being chosen for the bull ring.

DR. CASTLEMAN: Dr. Gordon Myers looked up some of the cases of fenestration that we had in our files. I think he found about 10 that were severe enough to be mentioned in the protocol, and none of them had any signs of aortic insufficiency.

DR. SPRAGUE: It is very interesting in relation to the development of cystic necrosis in young persons with dissecting aneurysms without hypertension. I wonder if that has some sort of congenital background?

DR. CASTLEMAN: Do young persons who develop dissecting aortic aneurysm have medionecrosis? I have never seen a case.

DR. SPRAGUE: Schnitker and Bayer[7] concluded, after extensive review of the literature and from their own experience, that the underlying lesion in both young and old patients was a degenerative cystic necrosis of the media.

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CASE 37502

PRESENTATION OF CASE

A twenty-five-year-old woman was admitted to the hospital because of chills, fever and abdominal pain.

Four days before admission, shortly after she had given herself an enema, she had a severe shaking chill that lasted only a few minutes. Thereafter she felt well until the following afternoon, when she had a second chill. Her temperature was 103°F. She developed mild persistent lumbar and lower-abdominal pain and pain on micturition. She was started on a course of aureomycin; as there was no improvement by the following day, sulfadiazine was added. The symptoms and temperature gradually subsided, but one hour before admission she had another episode of dizziness, chilliness and weakness.

Her general health had always been good. She had not previously had any urinary complaints. For one year she had been constipated. Until one month prior to entry, when she had menorrhagia with the passage of some blood clots, her menstrual periods had occurred regularly every 28 days and lasted 3 to 7 days. Because of the excessive flow, a dilatation and curettage was performed; the pathological report was "hyperplastic endometrium." Another menstrual period had begun a few days before admission. She had taken stilbestrol sporadically for painful recurrent lumps in the breasts but had not taken it for the four months prior to entry.

Four years prior to admission a left salpingo-oöphorectomy was performed; the pathological diagnosis was endometriosis. She had two operations in infancy — the first because of pyloric stenosis and the second ten months later for drainage of an abdominal abscess.

On physical examination the breasts were normal. The lungs were clear. There was a Grade II basal systolic murmur. The abdomen was soft and relaxed, without spasm or tenderness, and no organs or masses were palpable. There was no costovertebral-angle tenderness. Pelvic examination (which was deferred two days because of menstruation) showed a normal cervix and definite tenderness in

both right and left fornices and in the cul-de-sac, with the suggestion of a mass pressing on the bladder roof.

The temperature was 102°F., the pulse 114 and the respirations 24. The blood pressure was 140 systolic, 80 diastolic.

Examination of the blood revealed a white-cell count of 29,600 with 87 per cent neutrophils and a hemoglobin of 13.2 gm. The sedimentation rate was 34 mm. in 15 minutes and 56 mm. in 45 minutes. The nonprotein nitrogen was 16 mg. per 100 cc.

FIGURE 1.

Two blood cultures were negative. Urinalysis was negative and a culture showed no growth. Intravenous pyelogram showed prompt excretion by both kidneys, which were normal in position and contour. The renal pelves were larger than usual, the right more than the left. There appeared to be a constriction at both ureteropelvic junctions, and the emptying of the renal pelves was delayed so that after 60 minutes there was still considerable retention of the contrast material in both kidneys. There was the suggestion of a soft-tissue mass within the true bony pelvis, and the bladder was indented superiorly (Fig. 1); the left lower ureter appeared to be displaced somewhat laterally.

For the first three days in the hospital there was little change in the patient's condition. She complained of pain in the lower abdomen and lower back that radiated into the buttocks and was relieved by codeine. The temperature remained elevated to 101°F., with no marked fluctuations; the pulse varied between 100 and 125. On the fourth day there was an increase in the abdominal pain, with some localization in the right lower quadrant, and the patient vomited twice. On examination there was mild generalized abdominal tenderness but no spasm, and peristalsis was normal. The temperature spiked to 103°F. twice during that day. Penicillin and streptomycin therapy was begun. The following morning she was more comfortable but was nauseated. The abdomen was slightly distended and tympanitic and there was definite tenderness in the lower half. The temperature was 100°F. and the pulse 120. A plain film of the abdomen showed moderate gas accumulation in both small and large bowel, and there was a suggestion of a large soft-tissue mass almost completely filling the true pelvis. During the day the abdomen became progressively more distended. The patient began to belch considerable gas, the nausea increased and she vomited once. An enema returned very little gas and afforded no relief. By evening there was definite tenderness of the abdomen, most marked in the right lower quadrant, and there was definite resistance in the lower abdomen. Auscultation revealed severe medium-high-pitched tinkles in an otherwise quiet abdomen. Pelvic examination revealed a moderate sanguineous flow. There was distinct tenderness and a mass in the right vault; the left vault was normal. The temperature was 101.8°F. and the pulse 140. The white-cell count was 20,300, with 80 per cent neutrophils. Intestinal decompression resulted in some decrease in distention, but the abdominal tenderness increased and the temperature rose to 103°F. An operation was performed on the sixth day.

DIFFERENTIAL DIAGNOSIS

DR. LELAND S. MCKITTRICK*: Dr. Wyman, can you give me some help?

DR. STANLEY M. WYMAN: These films from an intravenous pyelogram show the kidneys to be nor-

*Visiting surgeon, Massachusetts General Hospital.

mal in size and shape. The fullness described in the renal pelvis is not very striking, and I think it can be considered within normal limits. The superior margin of the bladder is definitely indented by what appears to be a rather sizable soft-tissue mass (Fig. 1), but this is notoriously a difficult decision to make in many cases. I should not be surprised if the indentation was caused by the large bowel rather than by a large mass. The upright films again show indentation of the roof of the bladder. The films taken the next day show no significant change, and on the last film, taken two days later, there is definite distention of the small bowel, measuring up to 3 cm. in diameter. However, gas is present in the right colon and possibly in the rectum.

DR. MCKITTRICK: What about the mass described?

DR. WYMAN: The mass described is the central shadow in the pelvis. I would not be at all surprised, however, if a careful examiner told me that a pelvic examination was negative.

DR. MCKITTRICK: I thought the radiologist described a mass.

DR. WYMAN: The mass described was a small mass in the right vault that does not correspond to the central shadow.

DR. MCKITTRICK: Was that any larger five days later than it was the first day?

DR. WYMAN: I think one can consider the shadow essentially unchanged from the original examination.

DR. MCKITTRICK: You can see the sigmoid here, can you?

DR. WYMAN: I can see a small amount of gas in the center, perhaps lying in this fashion, probably in the sigmoid.

DR. MCKITTRICK: You do not see it higher than that?

DR. WYMAN: No; it is still confined to the true pelvis.

DR. MCKITTRICK: Let me summarize this case to make it clear in my mind. The real complaints were chilliness, dizziness and weakness. Four days before entry the patient took an enema and had a shaking chill. She was all right for twenty-four hours and then had another chill, some abdominal pain, not of much consequence, and pain on micturition. She had a temperature of 103°F., took antibiotics for three days and then had another attack of dizziness, chilliness and weakness just before she was admitted. She came directly to the hospital, where she was found to have a temperature of 102°F., a slight elevation of the pulse and a white-cell count of 30,000, with 80 per cent neutrophils; she had no anemia. Then her condition was much the same for three days; she developed a little lower-abdominal pain that went through to the buttock, pain enough to require codeine; the temperature went to 100°F.; the pulse was between 120 and 125. Four days before she came in, eight days after the onset, she had more abdominal pain, vomiting, distention and increased nausea. Then she began to have some generalized lower-abdominal tenderness, more or less localized in the right lower quadrant.

In this patient's past there is not too much of significance. Four years ago she had a left salpingo-oöphorectomy for endometriosis. One month ago a dilatation and curettage was done; I may be in error, but inasmuch as she had had a dilatation and curettage and the surgeons said she had hyperplastic endometrium and said nothing about the rest of the pelvis, I think that it is fair to assume that one month before admission she had a normal pelvis. On examination when she was admitted she had a normal abdomen. The physicians thought there might be a mass in the bladder roof. She had slight tenderness in both vaults and the posterior cul-de-sac. She had a high white count and a rapid sedimentation rate — I do not know much about sedimentation rates; we used to take them often, but they did not mean much to me, so I have not ordered one on a patient for fifteen years. I think this was elevated, but that does not help me make a diagnosis. The x-ray films you have just seen. I thought on reading the reports on these films that I could read into them that a questionable mass had become more definite on the last examination. Maybe I could assume there was increase in the size of the supposed soft-tissue mass. Now Dr. Wyman, in his helpful way, says he does not think I can assume that, but that possibly there is no mass and at any rate he does not see an increase in size. With the increase in symptoms the patient developed tenderness across the lower abdomen that became more marked on the right, and she then had what according to the record is an unquestionable mass in the right side of the pelvis and nothing in the left side of the pelvis.

I am not at all sure what this woman had. As a surgeon, seeing a patient who comes in with chills and fever, I immediately think of certain conditions. Among the more important ones are cholangitis, pylephlebitis and other types of infection in which showers of bacteria are thrown off into the blood stream — bacteremia or septicemia, if you want to call it such. In this woman pain has been a very minor problem. She obviously had a mass; it is clearly stated on the physical examination that it was found by the examiner. I think I can assume that the mass had increased in size, because when she first came in, when the abdomen was soft, relaxed and nontender, the physicians thought she had a mass in the roof of the bladder. Later, when she had tenderness and distention, they could definitely feel a mass in the right side. Regardless of the lack of help from Dr. Wyman and the Radiology Department, clinically I have a right to assume that the mass had increased in size. I am also assuming that there was no mass one month before her admission to the hospital. I therefore believe that this patient's primary lesion was in the pelvis; I suppose that the increase in size of the mass, the high white-cell count, the chills and the fever all point to an infection in that mass.

Now, having come that far, one begins to wonder "What can the mass be?" Well, the first thing one thinks of is the old endometriosis that was definitely proved pathologically four years before entry. I am going to eliminate endometriosis very simply, because in the first place I think it would be unusual for any acute episode associated with endometriosis to begin with chills and fever. I am also going to discard it by virtue of the fact that she had no mass there one week previously and a week later had a large mass. With or without justification, I am going to put endometriosis aside, as well as all other pelvic tumors.

That brings me down to some kind of abscess. Of course, the most common abscess in anybody at the age of twenty-five is an abscess secondary to appendicitis. In the old days probably an equally common abscess in a woman twenty-five years of age was the tubo-ovarian abscess; nowadays they are not so common. Another common cause of sepsis in the left side of the pelvis is a diverticulitis with perforation and local abscess formation. Its being on the right side of the pelvis is not a contraindication of that. It could be a diverticulitis of the cecum or diverticulitis associated with the loop of sigmoid that is on the right side of the abdomen. I have never seen diverticulitis progress to abscess formation in a patient of twenty-five. If it does occur, it occurs too infrequently to indicate logically that diverticulitis of the sigmoid was the diagnosis. A single diverticulum could possibly do it.

That leaves me floundering, — I am trying to make this as simple as I can, — between good old-fashioned tubo-ovarian abscess and appendiceal abscess. Since gynecology has been separated from the general surgical service, I have no idea how common tubo-ovarian abscesses are, and I presume that they are not really so common as they used to be, but I have a feeling that the gynecologists occasionally see one of these tubo-ovarian abscesses. This is not the classical onset for either. If I knew more about what happened after she was operated on, I could make a more clear-cut diagnosis. After she was operated on, if the operation was a corrective operation, I hope she did well. If that were so, I would probably make a diagnosis of tubo-ovarian abscess against an appendiceal abscess. If after operation she continued to have bouts of chills and fever, I would suppose the possibility of pylephlebitis was great and would change my diagnosis to an abscess secondary to appendicitis or possibly secondary to a diverticulitis. As I said, I have no strong conviction about the diagnosis; I believe that the most likely explanation, — because it is something that I have not seen for many years, — is a tubo-ovarian abscess.

Dr. Wyman: I would like to clarify my position with regard to the mass. I do think she had a mass. I was trying to point out that we have seen similar shadows when careful examination has proved that the patient had no mass. What can appear to be a mass by x-ray examination may prove to be an illusion. Did the surgeons take the appendix out when they operated on her previously?

Dr. Farahe Maloof: I think it is in the record.

Dr. Benjamin Castleman: Yes, according to the record the left ovary and tube and the appendix were removed. I am sorry that information was not in the abstract; it was not deliberately withheld.

Dr. Francis M. Ingersoll: Dr. McKittrick is entirely right in eliminating endometriosis as giving this picture. These can rupture and give a picture

that simulates acute appendicitis, but I have never seen it progress to cause a large inflammatory process such as this.

Dr. McKittrick: I have seen them rupture and cause an acute abdomen and high fever, but I have never seen one with recurrent chills and fever. Have you?

Dr. Ingersoll: No; I think you would be right in eliminating endometriosis.

Dr. Claude E. Welch: The mass appeared to change position in the pelvis, and in view of the fact that she had a perfectly normal period after the dilatation and curettage it seems unlikely that there could be trouble in the pelvic organs. I wonder about the possibility of disease in the small bowel, such as a regional ileitis.

Clinical Diagnosis

Small-bowel obstruction.

Dr. McKittrick's Diagnosis

Tubo-ovarian abscess.

Anatomical Diagnosis

Ruptured pyosalpinx with pelvic abscess.

Pathological Discussion

Dr. Castleman: At operation the surgeon found a small amount of cloudy fluid in the abdomen, and the small bowel was only moderately distended, but there were lower loops that lay in the pelvis and were firmly adherent. As they were separated a mass was found that was taken to be the right ovary. The surgeon believed the mass contained a necrotic endometrioma, 8 cm. in diameter, that had ruptured with the formation of a large pelvic abscess that extended across to the left side. He was able to separate the bowel from the ovary, and he then removed the mass. He was not able to identify the tube on that side. At one point the small bowel was adherent to the mass and was kinked; that would account for the mild degree of gas that was noted.

Dr. McKittrick: I had interpreted that gas as ileus because she had it in both large and small bowel.

Dr. Castleman: When we cut the mass it did not look very chocolate-like, as might be expected with endometriosis, but was purulent; our sections showed tubal epithelium with abscess formation. When tubal epithelium becomes infected it becomes markedly corrugated; hence in cutting across it one sees layers of epithelium that suggest endometriosis; in fact in this case it was first called endometriosis, but I do not believe that there was any evidence of endometriosis. This was a tubo-ovarian mass or just a pyosalpinx, since we could not identify any definite ovarian stroma.

Dr. Alfred Kranes: Were any organisms cultured?

Dr. Castleman: No cultures were taken.

Dr. Maloof: A vaginal culture was made from the dilatation and curettage.

Dr. Castleman: That was negative.

Further evidence that the right ovary or at least part of it had not been removed is the fact that the patient has continued to menstruate.

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THE *PRACTITIONER'S* MILESTONE

As THE first half of the wentieth century fades away, and the various observances that have commemorated its passage lapse into the shadows of the past, the London *Practitioner* steps into the center of the stage with its own authentic claim to that distinction that only time can give. For the October issue of the *Practitioner*, whose long and useful life of eighty-three years has already surpassed that of most medical journals, is also its thousandth — its millesimal number, as the hoary *Lancet* eruditely calls it.

The *Practitioner*, according to Sir Henry Dale, who has contributed its opening paper on "The Changing Face of Medicine," came into existence at a most significant moment. Medicine, because of its need for controlled experimental evidence and of knowledge of its use, was late in joining the modern scientific revolution. "But with the development of experimental physiology," as the *Lancet* relates it, "with the work of Pasteur on biogenesis and with Lister's application of it to antiseptic surgery, and with the discovery of X-rays, the medical revolution was well on its way; and the *Practitioner* was there to report."

This millesimal number contains also an account of "The Social Background of Medicine," with timely illustrations (reproduced from Punch) by Sir Henry Bashford; "Advances in Medicine" by Sir Henry Cohen, professor of medicine at the University of Liverpool; "Advances in Surgery" by Donald C. Balfour, emeritus professor of surgery of the Mayo Foundation, and a number of similar reports of the progress that has been made during these three and eighty years.

Perhaps the most interesting of all, however, — particularly to the author's many friends in America, — is the account of a hundred years of medical practice in a Yorkshire dale, by William N. Pickles, doctor of science as well as of medicine, rural practitioner extraordinary and medical officer of health of the Aysgarth Rural District Council.

In this reminiscent essay Dr. Pickles tells of four generations of physicians who had guided their horses or pedaled their bicycles or driven their cars through the lanes of Wensleydale — Matthew Willis, Alfred Baker, Edward Hime and, at the latest, himself and his partners. In it he mentions such ancient things as the local cure for dropsy, — *pellitory of the wall*, rooted in the crevices between the flat stones of which the Yorkshire villages are built, — and such modern things as an unusual little-publicized attitude toward the National Health Service when he reveals his own "feelings of delight and relief when I threw aside day book and ledger." For matters are different in Wensleydale, where, according to a patient, "Our doctor looks upon us all as members of his own big family."

Great as have been the advances in medicine that the *Practitioner* has recorded during these eighty-three years, they should not be purchased at the final cost of those human relations so faithfully cultivated by such practitioners as the doctor at Aysgarth.

COUNCIL OF NEW ENGLAND STATE MEDICAL SOCIETIES

THE fall meeting of the Council of New England State Medical Societies, held at the Copley Plaza Hotel in Boston on Sunday, November 18, seemed again to bear out the old adage that "the better the day, the better the deed." Certainly this was the best attended of a series of conferences that have been gaining in prestige and importance since the inception of the organization ten years ago.

The subject of the meeting, a "Symposium on Professional Relations in Medical-Care Insurance," no doubt accounted in part for the attendance, drawn from all six New England states.

Frank E. Smith, Ph.D., director of the national Association of Blue Shield Plans, told of the purposes of that organization, which are to help, like a trade association, in promoting understanding among the personnel of the 77 individual plans, with their 21,000,000 members and their gross earnings of $240,000,000. The association strives not only to assist the members with their problems but to improve their relations with the American Medical Association, a quarter of whose delegates are directors of Blue Shield plans.

Other speakers were Dr. Charles G. Hayden, executive director of the Massachusetts Blue Shield, on "Professional Relations in Blue Shield Plans"; John H. Miller, vice-president of the Monarch Life Insurance Company of Springfield, Massachusetts, on "Professional Relations in Medical-Service Insurance by Commercial Insurance Companies"; Dr. Charles L. Farrell of Pawtucket, Rhode Island, Dr. Joseph A. Holmes of Waltham, Massachusetts, and Dr. Daniel G. Sullivan of Nashua, New Hampshire, on "Medical-Service Insurance Plans Viewed by Practicing Physicians"; Dr. William H. Horton, managing director of Connecticut Medical Service, New Haven, Connecticut, on "The Structure of Fee Schedules in Medical-Service Insurance"; and Dr. Thomas J. Danaher, chairman of the Professional Policy Committee of Connecticut Medical Service, who summed up the symposium.

Although the matter of "catastrophic illness" was neither completely settled nor satisfactorily defined despite considerable discussion about it, and the care of the indigent was not even mentioned, the meeting helped toward the clarification of many points. Its value and interest were definitely increased by the presence and participation of a number of representatives of commercial insurance companies.

The dinner speaker, Dr. Louis H. Bauer, president-elect of the American Medical Association and secretary-general of the World Medical Association, spoke on socioeconomic problems as seen from an international point of view.

BERUTI ON PUERPERAL FEVER

DR. JOSUE BERUTI, professor of clinical obstetrics in the University of Buenos Aires, in 1947 published in the *Revista de la Universidad de Buenos Aires* a valuable monograph on the history of puerperal fever and the parts that were played in the discovery of its contagiousness by Holmes and Semmelweis.[1]

Beruti, after a study of the various theories propounded during the eighteenth and nineteenth centuries on the causation of the disease, concludes that to Holmes must go the honor of first propounding the theory of direct contagion from one person to another and to Semmelweis the credit for his clinical, experimental and prophylactic investigations. The two men worked independently, one in the United States and the other in Hungary, without knowledge of each other's studies.

During 1842 and the early part of 1843, an alarming number of cases of the disease occurred in Greater Boston, causing much concern to the members of the Boston Society for Medical Improvement. The matter was discussed at meetings of the society, and finally Dr. Holmes, then a young man, was requested to investigate the subject and make a report to the society at a future meeting. Holmes studied the cases and the available literature. He read his paper before the society on February 13, 1843, concluding that "the disease known as puerperal fever is so far contagious as to be frequently carried from patient to patient by physicians and nurses."[2]

Holmes's report was received without acclaim, and its printing was ordered in routine fashion.[3] It caused no furor at the meeting; one can imagine

that group of staid Boston physicians sitting around a large table calmly listening to a momentous declaration without realizing its great significance. Dr. Holmes had arrived by pure reasoning at his conclusion that the disease was contagious; he suggested seven prophylactic measures to be carried out by physicians attending obstetrical cases. However, he did not mention the use of antiseptics or disinfectants, therein failing to appreciate fully the practical possibilities in the control of the disease.

The publication of Dr. Holmes's paper aroused violent opposition to his theory in England and France, as well as in his own country —especially in Philadelphia, where two eminent physicians, Hugh L. Hodges, professor of obstetrics at the University of Pennsylvania, and Charles D. Meigs, professor of midwifery and the diseases of women and children in Jefferson Medical College, outspokenly opposed and even denounced Holmes's theory. As late as 1852 and 1854, Professor Hodges[4] and Professor Meigs[5] delivered addresses to their students on the non-contagiousness of the disease.

Dr. Holmes reprinted a few copies of his original paper soon after it appeared in 1843 in the *New England Quarterly Journal of Medicine*.[6] This periodical, which had a small distribution, flourished for only one year.

Dr. Holmes, who was at times rather stubborn, was stimulated by the addresses and letters of Hodges and Meigs to issue his second publication in the form of a pamphlet[7] that was copyrighted in 1855 by its publishers, Ticknor and Fields. Twenty pages are devoted to a further discussion of the disease; also included are a reprinting of the original paper of 1843 and two pages of additional cases and references.

In 1861 Semmelweis published his epoch-making book[8] on the etiology and prophylaxis of childbed fever and his concept of the disease. At the time he was a professor of theoretical and practical obstetrics at the University of Pest. Like Holmes he met with violent opposition from his fellow countrymen, but unlike Holmes he was ultimately ruined by it. The first 272 pages of the book are devoted to a discussion of the disease, in which it is stated that it is a form of pyemia and is contagious. Prophylactic measures are presented. Then follow 264 pages devoted to correspondence and material concerning the literature for and against his theory, from twenty-eight eminent physicians.

Semmelweis was also stimulated to answer his detractors; he did so in three pamphlets entitled "Open Letters."[9-11]

It is interesting to note that as early as 1789 a thesis on puerperal fever was presented to the University of Cambridge in America (Harvard) for the degree of bachelor in medicine, by Peter de Sales la Terrière, of Canada.[12]

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7. *Puerperal Fever as a PrivatePestilence.* 60 pp. Boston: Ticknor and Fields, 1855. (The Library has an autographed copy presented to Dr. Henry J. Bigelow, who evidently co-operated with Dr. Holmes during the controversy. The text is marked throughout with corrections and suggestions by Dr. Bigelow and indicates proposed further publication. However, Dr. Holmes dropped the matter for other interests.)
8. Semmelweis, I. P. *Die Aetiologie, Begrif und die Prophylaxis des Kindbettfiebers.* 544 pp. Pest, Wein and Leipzig: C. A. Hartleben, 1861.
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10. *Idem.* Zwei offene Briefe an Hofrath Dr. Eduard Casp. Jac. v. Siebold, Professor der Geburtshilfe zu Göttingen, und an Hofrath Dr. F. W. Scanzoni, Professor der Geburtshilfe zu Würzburg. 40 pp. Pest: Gustav Emich, 1861.
11. *Offener Brief an sämmtliche Professoren der Geburtshilfe.* 92 pp. Osen Königl. ungar. Univ. Buchdruckerie, 1862.
12. de Sales la Terrière, P. A. *A Dissertation on the Puerperal Fever.* 18 pp. Boston, 1799. (A copy is in the Library.)

RHEUMATIC FEVER SERVICES

A NEED, long felt by many physicians, should be met by the new co-ordinating service for rheumatic-fever patients, announced in these pages. Although the most important of the many requirements of rheumatic-fever patients are probably medical in nature, other needs, — social, economic and educational, — must be met if the patient is to conquer fully all the effects of the disease.

In the development of this function the Rheumatic Fever Services Committee of the Massachusetts Heart Association has conducted a year-long quantitative and qualitative study of Greater Boston's facilities for meeting the basic requirements of all rheumatic-fever patients. This study showed that the community is rich in resources for the care of such patients but that the individual patient rarely receives all the help and care that could have been made available to him.

In essence, the new project may be described as a clearing-house device to ensure that every patient receives the benefits of as many of the existing services as he needs.

For example, a patient might have received the best of care during the acute and convalescent stages of his illness, only to be returned to a family who lacked understanding of his problem or to a home in which he had to share a bed with another child or was not even adequately fed. Some or all of these shortcomings could usually have been remedied if the services of one or more of the available agencies had been used.

Although neither the Rheumatic Fever Services Committee nor the Red Feather Information Service is in a position to supply beds for patients, both agencies, — and particularly the Red Feather Information Service, — are in close touch with agencies whose business it is to provide these things. The co-ordinating service will make proper referrals and provide sufficient follow-up to see that such needs are met. This is a refreshing example of close co-operation in spirit and in word between a specialized voluntary health association and the agency responsible for meeting the social, economic and educational needs of Greater Boston.

It can safely be said that very few rheumatic-fever patients are now receiving all the basic needs as defined by the committee and listed in the announcement; physicians are urged to register such cases with the agencies mentioned.

An impression is entertained by the public, that physicians are less friendly towards each other, than gentlemen of the professions of law and divinity.

Boston M. & S. J., *December 17, 1851*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

CAMOESAS — Joao J. C. Camoesas, M.D., of Taunton, died on November 11. He was in his sixty-fifth year.

Dr. Camoesas received his degree from the University of Lisboa Faculty of Medicine in 1925.

His widow and three sons survive.

CRAWFORD — G. Marshall Crawford, M.D., of Lincoln, died on October 19. He was in his forty-sixth year.

Dr. Crawford received his degree from Northwestern University School of Medicine in 1932. He was a member of the American Dermatological Association, the American Academy of Dermatology and Syphilology, the Atlantic Dermatological Society and the American Cancer Society; at the time of his death he was president and secretary of the New England Dermatological Society.

His widow survives.

DOWNEY — Charles J. Downey, M.D., of Springfield, died on November 24. He was in his eighty-third year.

Dr. Downey received his degree from the University of Vermont College of Medicine in 1892. He was a member of the Springfield Academy of Medicine and the Massachusetts Tuberculosis Association.

A son and a daughter survive.

ORDWAY — Mabel D. Ordway, M.D., of Jamaica Plain, died on November 27. She was in her seventy-eighth year.

Dr. Ordway received her degree from Tufts College Medical School in 1905. She was a member of the New England Women's Medical Society and a former secretary of the American Psychiatric Society.

A daughter survives.

SIMMONS — Hugh L. Simmons, M.D., of Worcester, died on November 20. He was in his fifty-ninth year.

Dr. Simmons received his degree from Tufts College Medical School in 1916. He was a member of the New England Obstetrical and Gynecological Society and the Association of Military Surgeons of the United States.

His widow and three sons survive.

NOTES FROM THE MEDICAL EXAMINER*

ACUTE PULMONARY EDEMA DUE TO ASPIRATION OF GASTRIC JUICE

Regurgitation and aspiration of stomach contents may cause serious complications in old and infirm patients, in those who are unconscious, regardless of the cause, and in those suffering from some abnormality of deglutition. Suffocation incident to massive aspiration may lead to acute asphyxial death. If the amount aspirated has been smaller, pulmonary abscesses, bronchiectasis, pneumonia or atelectasis may result. These are well recognized complications. One that is relatively unrecognized is chemical pneumonitis from aspiration of gastric juice *per se* without other foreign material.[1] Symptoms appear after a latent period of several hours. They consist initially of dyspnea and later of cyano-

*Presented by the Department of Legal Medicine, Harvard Medical School.

sis; these become progressively severe. Death from inhaled gastric juice during the first twenty-four to forty-eight hours is caused by hemorrhagic pulmonary edema due solely to the irritating effect of hydrochloric acid on the alveolar capillaries.

It should be emphasized that the only component of filtered gastric juice that is to be regarded as pathogenetic is the free acid present. Neutralized gastric juice is harmless when instilled into the trachea of rabbits, whereas dilute solution of hydrochloric acid in normal saline solution causes results comparable to that caused by gastric juice of similar acidity.[2]

Localization of hydrochloric-acid injury in the pulmonary parenchyma is dependent on differences in the susceptibility of bronchial and alveolar epithelium to alteration by the chemical. A concentration of the acid that may be inadequate to cause severe damage to bronchial and bronchiolar mucosa

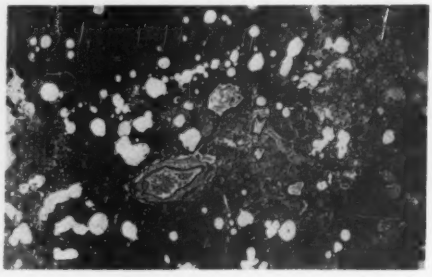

FIGURE 1. *Hemorrhagic Pulmonary Edema following Aspiration of Gastric Juice (Case 2).*
The extent of intra-alveolar hemorrhage is unusually severe. (Hematoxylin and eosin, x27.)

may still be sufficiently high to damage the more delicate endothelium of the alveolar capillaries. Centrally located pulmonary lobules are more likely to sustain severe injury than are those that are peripherally situated, as, in the former, alveolar ducts and communicating alveoli have the shortest and most direct connections with the bronchi at the hilum.

The sequence of events is essentially the same as that following gassing by irritating chemicals such as oxides of nitrogen, acrolein, phosgene and halogens. There is direct primary chemical injury of the endothelium of the alveolar capillaries. As a result of the increased permeability, fluid leaks into the alveolar spaces. This fluid becomes progressively richer in protein and ultimately hemorrhagic as the endothelial damage increases.

In fatal cases the lungs are heavy, voluminous and waterlogged. From the red to purple sectioned surfaces, copious quantities of pinkish froth may exude; similar material may occupy the trachea and oropharynx. If autopsy is performed soon after death, bronchial and lung fluid may be acid as shown by reaction with nitrazine paper. In the event that death does not take place in short order as a result of the acute condition, the damaged epithelium may constitute the portal of entry for secondary bacterial infection.

Treatment during the acute stage should consist of pure oxygen with 5 per cent carbon dioxide added. An objective should be prevention of secondary bacterial pneumonia by administration of antibiotics.

CASE REPORTS

CASE 1. A 28-year-old woman, para ii, was given ether anesthesia. About 12 to 15 hours after uneventful delivery of a normal infant the patient became progressively dyspneic and cyanotic. Aspiration of the air passages and supportive treatment did not alter her course, and she died 24 hours later. The lungs showed extensive focal and confluent hemorrhagic edema. The pH of the bronchial fluid was 6.7.

CASE 2. A man showed catatonic schizophrenia with increasing hyperexcitement and uncontrollable activity. On transfer to the medical service he showed peripheral circulatory collapse. There was hemoconcentration and acidosis. He died with no specific cause of death being shown. The immediate cause of death was heavy, wet lungs weighing 2000 gm. that showed focal and confluent hemorrhagic consolidation, especially in central areas. Fifteen hours after death the bronchial fluid showed a normal pH. There was desquamation of epithelium in bronchi and bronchioles, particularly in the former, and an early exudative reaction in the peribronchial tissue. Foreign débris was present in the lumen. Microscopical examination showed severe intra-alveolar edema and hemorrhage (Fig. 1).

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W. W. JETTER, M.D.
Professor of Legal Medicine, Boston University School of Medicine; Lecturer in Legal Medicine and Toxicology, Tufts College Medical School.

CORRESPONDENCE

INTRADERMAL ANESTHESIA IN FIRST-STAGE LABOR

To the Editor: In 1950 Abrams[1] reported his experience in ablating the referred pain of uterine contractions in the first stage of labor by means of intradermal injections of an anesthetic agent. Since that time, other reports have appeared that demonstrate the results of this "new" method of relieving pain in the first stages of labor. In this connection a historical and clinical review of the subject may be of interest.

In his paper Abrams refers to a previous publication as follows: "In 1928, Rose[2] described the successful intradermal use of novocain to break the pain reference arc in the first stage of labor." It should be noted that the 1928 reference was a preliminary report made to establish priority of an original investigation. In 1929, I published in the *New England Journal of Medicine* my final report[3] on the use of my original method in 100 unselected cases from the Obstetric and Gynecologic Clinic of the Boston City Hospital. This publication related in detail the experimental method employed in determining the areas to be infiltrated intradermally with an anesthetic agent to break the arc of referred pain. This was followed by a description of the detailed technic of infiltration and an analysis of the results in the 100 cases studied. It is to be regretted that Abrams completely over-

looked the final report of the *original* investigation as published in 1929.

A comparative analysis and review of my 1929 report and the 1950 Abrams report demonstrates several interesting points:

Abrams corroborated the original lines of infiltration in the lower lateral segments and further emphasized my observation that the infiltration must be intradermal to be successful. These lateral lines are identical in both papers. Abrams deviated in his choice of the longitudinal zone. I used a "longitudinal area, or more truly, a line which extends almost from the height of the fundus down to just above the umbilicus." Abrams' variation is to extend the longitudinal area from the symphysis upwards toward the umbilicus. I found that infiltration (of the back) gave only partial relief of back pain. This was confirmed by Abrams. I used 2 per cent novocain; Abrams used procaine, pontocaine and metycaine. Therefore, as I compare the technics I find that Abrams employed two modifications of the original method, namely metycaine as the anesthetic of choice and the change of locale of the longitudinal area of infiltration. These modifications were obviously made in an attempt to improve the results obtained by me. I should like, therefore, to compare and analyze the results reported in both papers.

I reported on 100 cases, unselected. Abrams reports on 40 cases, partially selected (private patients who consented to the use of infiltration). I noted that 94 per cent of patients had complete relief of abdominal pain. Abrams reported 22 cases, or 55 per cent, with complete relief. I reported 6 per cent failures, and Abrams 3 cases, or 8 per cent failures. I classified any patient who had less than two hours of relief as a failure. I further stated: "There were no other medications or anesthetics employed." I relied solely on intradermal infiltration for relief in the first stage of labor. Abrams, on the other hand, used additional forms of analgesia in 11 cases. Thus, to truly evaluate the results of Abrams' modification, only 29 cases, rather than 40, should be considered — or, more correctly, those 11 cases should be classified as failures because additional methods of pain relief became necessary.

The comparative analysis therefore demonstrates either that metycaine, as employed, does not improve the results obtained with 2 per cent novocain or that the change in zones of infiltration is responsible for Abrams' failure to improve on my results.

Thus, my original prior work has been corroborated, and the changes made by Abrams have failed to produce better results and, in fact, resulted in a slightly higher percentage of failures and a significantly smaller percentage of cases of complete relief (2 per cent and 39 per cent respectively).

It is hoped this communication will help to rectify the omission of mention of the prior investigation, and it is suggested that further trial of this method is indicated. It is also suggested that the original zones of infiltration with an anesthetic agent of significantly longer duration than the 2 per cent novocain originally used may produce better results in terms of duration of relief.

David Rose, M.D.
Chief of gynecology
Mount Auburn Hospital
Cambridge, Massachusetts

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BOOK REVIEWS

Meister der Chirurgie und die Chirurgenschulen im deutschen Raum: Deutschland, Osterreich, Deutsche Schweitz. By Prof. Dr. H. Killian and G. Kramer. 8°, cloth, 232 pp., with 32 illustrations and 10 tables. Stuttgart: Georg Thieme, 1951. DM 24.80.

Professor Killian, when working on his monograph on narcosis during the period 1930-1934, became interested in the history of surgery; this led him to write this outstanding history of the art in German-speaking countries (Germany, Austria and German Switzerland).

The first chapter is devoted to a short historical survey of surgery from the time of Constantinus Africanus of Salerno (1060 A.D.) to the establishment of the German Society of Surgery, under Langenbeck and Volkmann in 1872, one year after the founding of the German Reich.

The history of Germany proper during the last two hundred years is developed along unique lines. It is arranged according to universities, beginning with Prague (1348) and ending with Danzig (1933). The new Free University of Berlin, West Sector (1950), has not lived long enough to develop a history. There is a brief historical sketch of each university, followed by short biographies of outstanding surgeons. This portion of the book, over three fourths of the text, contains a mine of information on eminent German surgeons.

Concluding the text, there is a genealogy of the German surgical schools (families), beginning with Karl Kaspar von Siebold (Würzburg 1776-1807), the founder of the German dynasty of surgeons, to the modern school of Georg F. L. Stromeyer (Freiburg, 1842-1849). To one familiar with German surgery, these charts are interesting in their perspective, the prominent names standing out like mountain peaks and emphasizing the great tradition of Germany in the field of surgery. There is a short bibliography and an index of names. There are portraits of 32 eminent men, from Albertus Magnus (1193-1279) to Theodor Kocher (1841-1917).

The publishing is excellent, and the monograph is essential for all historical collections.

James F. Ballard

The Integration of Psychiatry and Medicine: An orientation for physicians. By William B. Terhune, M.D. 12°, cloth, 177 pp. New York: Grune and Stratton, 1951. $2.75.

As a pilot experiment the author served as visiting chief *pro tempore* in the medical service of the Atlantic City (New Jersey) Hospital, in an attempt to orient the non-specialist practitioner and house staff in psychiatry. The choice of teacher was fortunate, as Dr. Terhune has long been recognized for his psychiatric erudition and his ability to present his ideas in an instructive manner. The non-university general hospital used was also representative of an excellent small unit. This book grew out of the experiment. As a brief review of psychiatry as practiced today, with due consideration of psychodynamics, psychotherapy and psychosomatic medicine, the book offers much. It is well written and skillfully presented; only minor criticisms are justified. Many readers will consider psychoanalysis unduly emphasized. Drug doses are sometimes given in apothecaries' measures, at other times according to the metric system. A brief list of references to the important literature would be a useful addition; only a few books are noted. The final chapter on medical ethics, although of interest, seems a little out of place in a book of this type.

Henry R. Viets, M.D.

The Neuroses: Diagnosis and management of functional disorders and minor psychoses. By Walter C. Alvarez, M.D. 12°, cloth, 667 pp. Philadelphia: W. B. Saunders Company, 1951. $10.00.

The author, for many years an internist at the Mayo Clinic, has long taken a special interest in the diagnosis and treatment of functional disease. His experience has been extensive. A keen student of human nature and with a personality well suited to inspire confidence, Dr. Alvarez now summarizes his observations in a long, rambling, discursive and frequently repetitious book. The style is conversational; the personal pronoun occurs in almost every line; expressions such as "clear up beautifully," "all they get for their money," and "blowing in ten dollars' worth of energy" are to be found in nearly every page. By digging in, however, a rich store of good common sense can be found. The author's plea for better recognition of the neurosis is sound and welcome. His simplified types of personality, the chapters on causes and recognition and particularly the section on the psychosomatic features of the specialties of medicine are well done and impressive. The book would be vastly improved by rigid pruning. Much of the material has appeared in periodicals.

An appendix lists state mental-hygiene societies, commitment procedures and state mental-health authorities. An excellent bibliography and index are included.

HENRY R. VIETS, M.D.

Diabetes Mellitus: Principles and treatment. By Garfield G. Duncan, M.D. 8°, cloth, 289 pp., with 31 illustrations and 40 tables. Philadelphia: W. B. Saunders Company, 1951. $5.75.

This is a good book for either physician or diabetic patient. Its author, an experienced teacher and a skillful physician, expresses his ideas clearly. Moreover, Dr. Duncan's knowledge of diabetes was enriched by his early association with Dr. Frederick M. Allen, whose influence is revealed in this monograph. The book is heartily recommended by the reviewer.

ELLIOTT P. JOSLIN, M.D.

Breast Deformities and Their Repair. By Jacques W. Maliniac, M.D. 8°, cloth, 193 pp., with 119 illustrations. New York: Grune and Stratton, 1950. $10.00.

Mammaplasty is a relatively new field, and its popularity has been progressively increasing in the past twenty-five years. Reconstructive operations on the female breast are performed for the purpose of reducing its size and improving its shape. The author believes that "few reconstructive procedures afford greater physical and psychic relief."

This book of 193 pages discusses the many aspects of mammaplasty. The first chapters give a historical review, which is followed by a good discussion of the anatomy of the breast and the symptomatology of the ptosed breast. The most important chapters are VI and VII, in which the author describes not only the surgical procedures that he prefers at present but also the procedures of other surgeons who have made important contributions in this field of plastic surgery. The general aim is to improve the contour and the size of the breast without sacrificing its main function, lactation.

The author admits that in some respects, even though there is a great amount of medical literature on the subject, mammaplasty is still largely in its pioneer stage. The book is very readable and contains many diagrams and photographs. Each chapter is supplemented with well chosen references. This reviewer considers the book a valuable volume for those interested in this branch of plastic surgery.

V. H. KAZANJIAN, M.D.

BOOK RECEIVED

The receipt of the following book is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Growth and Development of Children. By Ernest H. Watson, M.D., associate professor, and George H. Lowrey, M.D., instructor, Department of Pediatrics and Communicable Diseases, University of Michigan Medical School. 8°, cloth, 260 pp., with 54 illustrations and 41 tables. Chicago: The Year Book Publishers, Incorporated, 1951. $5.75.

This manual is based on the work done in the Department of Pediatrics at the University of Michigan and is supplemented by a survey made among teachers of pediatrics and public health. The material embraces the fetus, the body and the organs. There are also chapters on behavior development, energy metabolism and nutrition in normal growth. Lists of references are appended to various chapters and there is a good index. The volume should be in all collections on pediatrics.

NOTICES

SCHOOL OF CYTOLOGY

The Cancer Cytology Center of the Dade County Cancer Institute, an affiliate of the Medical Research Foundation of Dade County in Miami, Florida, has announced its first one-week seminar for physicians to be held at the Institute January 14-19, 1952.

Further information concerning qualifications, registration, fees and other details may be obtained from the director of the Dade County Cancer Institute, 1155 North West 14th Street, Miami, Florida. Applications for registration, limited to 35 physicians, will be accepted through January 12, 1952.

LOUIS LEFKOE MEMORIAL FOUNDATION

The Louis Lefkoe Memorial Foundation offers a prize of $500 for the most worth-while original contribution to the medical knowledge of cerebral palsy.

The paper is to be in the customary format for publication of medical literature. It may cover any aspect of the subject, such as pathogenesis, biochemical knowledge, pathology, diagnosis, treatment and so forth. Papers must be submitted to the trustees of the foundation on or before September 1, 1952. The prize is open to anyone who can contribute to the medical knowledge of the subject.

Further information can be obtained by writing to the Louis Lefkoe Memorial Foundation, 601 Medical Arts Building, Sixteenth and Walnut Streets, Philadelphia 2, Pa.

SOUTH END MEDICAL CLUB

The next luncheon meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, on December 18, at 12 m.

The speaker will be Dr. Ray E. Ebert, chief resident, Fifth Surgical Service, Boston City Hospital. His subject will be "Shock and Its Treatment."

HELEN PUTNAM FELLOWSHIP

Radcliffe College offers for the academic year 1952-1953 the eighth Helen Putnam Fellowship for Advanced Research. This is a postdoctoral resident fellowship for women in the field of genetics or of mental health, broadly defined as including such fields as clinical psychology and child development. The award carries a grant of $3000 a year, with the possibility of renewal.

Applications should be returned to the Secretary of the Graduate School, Radcliffe College, Cambridge, Massachusetts, not later than April 1, 1952. Preference will be given to those whose research is already in progress.

NEW ORLEANS GRADUATE MEDICAL ASSEMBLY

The fifteenth annual meeting of the New Orleans Graduate Medical Assembly will be held in New Orleans from March 10 to 13, 1952, with headquarters in the Municipal Auditorium.

The program will include symposia on "Resuscitation" and "Complications of Antibiotic Therapy and Their Management," daily demonstrations of medical and surgical procedures in color television, clinicopathological conferences, medical motion pictures, over 100 technical exhibits and three round-table luncheons. Eighteen outstanding guest speakers will participate in the Assembly.

A postclinical tour by plane to Merida, Yucatan, Mexico, Cuernavaca, Taxco and Acapulco will be conducted from March 15 to 29.

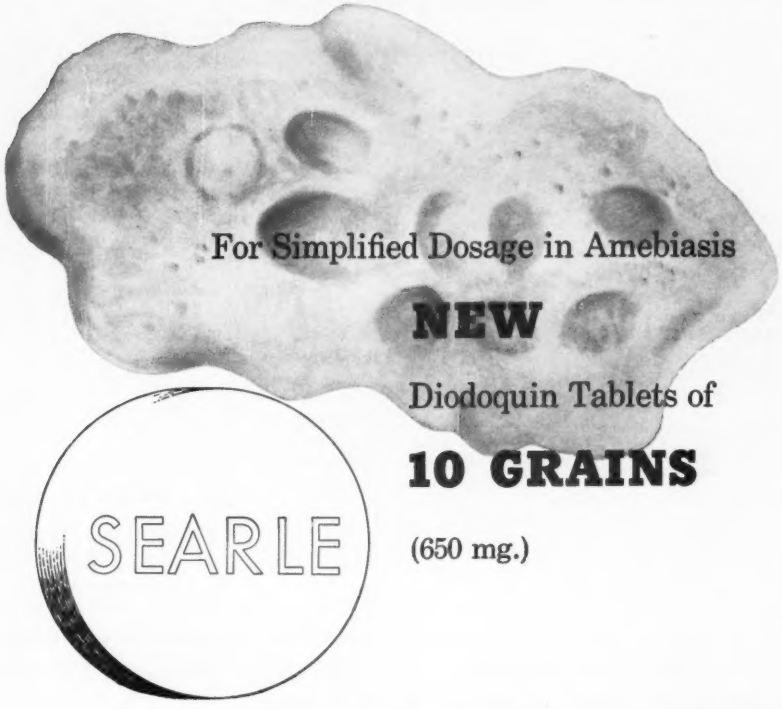
Details of the New Orleans meeting and the tour are available at the office of the Assembly, Room 103, 1430 Tulane Avenue, New Orleans 12, Louisiana.

MASSACHUSETTS HEART ASSOCIATION

Increased assistance to physicians in securing necessary services for their rheumatic-fever patients was made available on November 1 through the joint efforts of the Red Feather Information Service of the United Community Services and the Massachusetts Heart Association.

Physicians are urged to telephone or write to the Red Feather Information Service at 14 Somerset Street (RIchmond 2-2000) or the Massachusetts Heart Association, 650 Beacon Street (COpley 7-4400), for further information.

(*Notices concluded on page xv*)



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NOTICES (*Concluded from page 956*)

SOCIETY MEETINGS AND CONFERENCES

DECEMBER 14, 21 AND 28 AND JANUARY 4. New England Deaconess Hospital Clinic. Page 548, issue of October 4.

DECEMBER 15–22. The Springfield Hospital. Page 832, issue of November 22.

DECEMBER 14–JANUARY 4. New England Deaconess Hospital Clinics. Page 548, issue of October 4.

DECEMBER 14 AND 15. Association for Research in Nervous and Mental Disease. Page 958, issue of June 21.

DECEMBER 18. South End Medical Club. Page 956.

DECEMBER 28. Symposium on Premedical Education. Page 916, issue of December 6.

JANUARY 7, FEBRUARY 25 AND APRIL 15. Massachusetts Society for Research in Psychiatry. Page 792, issue of November 15.

JANUARY 9. Essex North District Medical Society. Page 832, issue of November 22.

JANUARY 10. The Recognition and Management of Common Kidney Diseases. Dr. Robert P. McCombs. Pentucket Association of Physicians, 8:30 p.m. Haverhill.

JANUARY 14–19. School of Cytology. Page 956.

JANUARY 22, FEBRUARY 26, MARCH 25 AND APRIL 24. Norfolk District Medical Society. Page 710, issue of November 1.

JANUARY 23. Suffolk District Medical Society. Page 669, issue of October 25.

MARCH 10–13. New Orleans Graduate Medical Assembly. Page 956.

MARCH 12. Northeastern New York Radiological Society. University Club, Albany, New York.

MARCH 31–April 4. Fifth American Congress on Obstetrics and Gynecology. Page 832, issue of November 22.

MAY 1–3. American Goiter Association. St. Louis, Missouri.

JULY. Commonwealth and Empire Health and Tuberculosis Conference. Page 792, issue of November 15.

JULY 8–11. Thirteenth British Congress of Obstetrics and Gynaecology. Page 916, issue of December 6.

JULY 14–19. International Congress of Physical Medicine. Page 998, issue of June 28.

SEPTEMBER 7–9. Combined session of the New Hampshire and Vermont State Medical Societies, Mount Washington Hotel, Bretton Woods, New Hampshire.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH

JANUARY 9. Pentucket Club, 111 Main Street, Haverhill.

HAMPSHIRE

JANUARY 2. Veterans Hospital, Northampton.
MARCH 5. Cooley-Dickinson Hospital, Northampton.
MAY 7. Annual Meeting. Jones Library, Amherst.

NORFOLK

JANUARY 22. Veterans Administration Hospital, West Roxbury.
FEBRUARY 26. Boston Medical Library.
MARCH 25. Boston Medical Library.
APRIL 22. Boston Medical Library.
MAY 7. Place to be announced.

SUFFOLK

JANUARY 23. Massachusetts General Hospital.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, DECEMBER 20

THURSDAY, DECEMBER 20

*9:00–10:00 a.m. Grand Rounds. Robert Breck Brigham Hospital.
*12:00 m.–1:00 p.m. Guest speaker. Stearns Auditorium, New England Center Hospital.
*4:00–5:00 p.m. Medical Division Lectures. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. X-Ray Conference. Mount Auburn Hospital, Cambridge.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Amphitheatre, New England Deaconess Hospital.

FRIDAY, DECEMBER 21

*8:15 a.m. Childhood Diabetes. Drs. Brown and White. Baker Clinic, New England Deaconess Hospital.
*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street.
*11:00 a.m.–12:00 m. Pediatrics. Woolson II. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. New England Center Hospital.
*12:00 m.–1:00 p.m. Tumor Conference. Pratt Lecture Hall. New England Center Hospital.
*1:00–2:00 p.m. Tumor Clinic, Mount Auburn Hospital, Cambridge.

MONDAY, DECEMBER 24

*11:30 a.m.–12:15 p.m. Clinical Conference. South End Health Unit, 57 East Concord Street. Dr. Cleaveland Floyd in charge.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheatre, Peter Bent Brigham Hospital.
3:00–4:00 p.m. Gynecology Rounds. Mount Auburn Hospital, Cambridge.
*7:00–9:00 p.m. Combined Anesthesia Teaching Program of Boston. Stearns Auditorium, New England Center Hospital.

WEDNESDAY, DECEMBER 26

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street.
*12:00 m.–1:00 p.m. Clinicopathological Meeting. Mount Auburn Hospital, Cambridge.
12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheatre, New England Deaconess Hospital.

*Open to the medical profession.

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